Southern Medical Journal

JOURNAL OF THE SOUTHERN MEDICAL ASSOCIATION

VOL. 52 AUGUST 1959 NO. 8

In this issue—

THE PROBLEM OF HEMORRHAGE FOLLOWING MASSIVE TRANSFUSIONS—Robert M. Bird and James F. Hammarsten 887

DIVERTICULUM OF THE FEMALE URETHRA: WITH SPECIAL REFERENCE TO DIVERTICULAR CARCINOMA—William Niles Wishard, Jr., Myron H. Nourse, and John H. O. Mertz 890

DIAGNOSIS AND TREATMENT OF INJURIES TO THE LUMBAR INTERVERTEBRAL DISK OF INDUSTRIAL WORKERS—Homer D. Kirgis and Raeburn C. Llewellyn 895

CASE REPORT

HUMAN LEPTOSPIRAL INFECTION DUE TO ONE OF THE *LEPTOSPIRA AUSTRALIS A* GROUP: REPORT OF A CASE IN THE UNITED STATES—John Ammons, Mildred M. Galton, L. E. Starr, R. W. Menges, and Charles LeMaistre .. 900

HEMOLYTIC ANEMIA IN CIRRHOSIS—Leslie Zieve and Earl Hill 903

CASE REPORT

ACUTE PULMONARY HISTOPLASMOSIS—Glenn E. Horton, John C. Larkin, and Samuel Phillips 912

INTUSSUSCEPTION IN CHILD AND ADULT—A COMPARISON—George B. Sanders and David W. Kinnaird 920

ANTICHOLINERGIC ANESTHESIA—Clarence W. Legerton, Jr. 927

LIMBIC TUMORS—Jerome L. Byers 932

CONTRIBUTIONS OF INTRALUMINAL PRESSURE MEASUREMENTS TO OUR UNDERSTANDING OF ESOPHAGEAL DISORDERS—Joseph H. Stickley, E. Clinton Texter, Jr., Clifford J. Barborka, Hubbard W. Smith, and Gaston Vantrappen 936

OSTEOCHONDRITIC CHANGES IN THE HEAD OF THE FEMUR AFTER REDUCTION OF CONGENITAL DISLOCATION OF THE HIP—J. Hiram Kite 945

Continued on cover 2

Fifty-Third Annual Meeting, November 16-19, 1959, Atlanta, Georgia

AUGUST 1959

VOLUME 52 NUMBER 8

Southern Medical Journal

JOURNAL OF THE SOUTHERN MEDICAL ASSOCIATION

STAFF

Editor
R. H. Kampmeier, M.D.

Managing Editor
V. O. Foster

Business Manager
Robert F. Butts

EDITORIAL BOARD

Surgery
William F. Reinhoff, Jr., M.D.

Neurology
Psychiatry
Sullivan G. Bedell, M.D.

Orthopedics
Lenox D. Baker, M.D.

Proctology
Curtice Rosser, M.D.

Obstetrics
Gynecology
Willis E. Brown, M.D.

Pediatrics
Preston A. McLendon, M.D.

Urology
Charles Rieser, M.D.

Dermatology
John H. Lamb, M.D.

Pathology
J. F. A. McManus, M.D.

General Practice
Stanley A. Hill, M.D.

OFFICERS

President
Milford O. Rouse, M.D.

President-Elect
Edwin H. Lawson, M.D.

First Vice-President
Tom D. Spies, M.D.

Second Vice-President
Edwin L. Zander, M.D.

Published monthly by the Southern Medical Association, 2601 Highland Avenue, Birmingham 5, Alabama. Annual subscription, $10.00. Single copies, $1.00 each. **Copyright, Southern Medical Association, 1959.**

Entered as second-class matter at the Post Office at Birmingham, Alabama, under Act of March 3, 1879. Acceptance for mailing at special rate of postage provided for in Section 1103, Act of October 3, 1917, authorized December 20, 1921.

CONTENTS

Continued from cover 1

THE HAZARDS OF RADIUM ACCIDENTS—H. Stephen Weens and R. H. Rohrer 952

MEDICOLEGAL ASPECTS OF ANESTHESIOLOGY—A. J. Ochsner II 958

TYMPANOPLASTY CLASS III IN TEACHING MASTOIDECTOMY OPERATIONS—George D. Lyons 961

FOUR YEARS EXPERIENCE WITH A COBALT UNIT—Patrick Cavanaugh 964

FURTHER OBSERVATIONS ON THE PROBLEMS OF VESICOURETERAL REFLUX—C. M. Pasquier, Jr., E. C. St. Martin, and J. H. Campbell 967

CASE REPORT

BRONCHOPULMONARY MONILIASIS COMPLICATED BY PERITONITIS: EVALUATION OF TREATMENT OF ACUTE BRONCHOPULMONARY MONILIASIS—Lawrence Maryanov 975

QUINACRINE IN THE TREATMENT OF DISCOID LUPUS ERYTHEMATOSUS: A FIVE YEAR FOLLOW-UP SURVEY—RESULTS AND EVALUATION—Robert N. Buchanan, Jr. 978

A NOTE ON HYDROCHLOROTHIAZIDE AS A THERAPEUTIC AGENT—Tom D. Spies, William Niedermeier, and Robert E. Stone 984

CITRATED CALCIUM CARBIMIDE IN THE TREATMENT OF THE ALCOHOLIC—Merritt W. Foster, Jr. 986

PANCREATITIS: A TWELVE YEAR REVIEW—Benjamin B. Weisiger 988

EDITORIALS 993

The Uses of the Past

Dermatomyositis and Malignancy

TWENTY-FIVE YEARS AGO 995

SOUTHERN MEDICAL NEWS 996

BOOKS RECEIVED 997

INSTRUCTIONS TO CONTRIBUTORS 997

BOOK REVIEWS 998

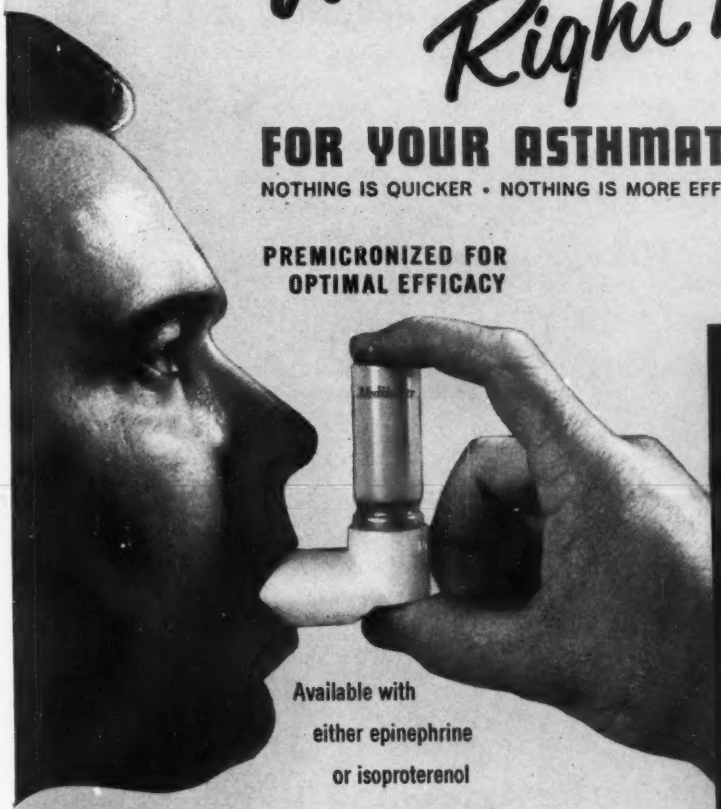
OFFICERS OF THE SOUTHERN MEDICAL ASSOCIATION 1958-1959 1000

22½% More Vital Capacity Right Now

FOR YOUR ASTHMATICS

NOTHING IS QUICKER • NOTHING IS MORE EFFECTIVE

PREMICRONIZED FOR OPTIMAL EFFICACY



Available with either epinephrine or isoproterenol

automatically measured-dose aerosol medications

Nonbreakable • Shatterproof • Spillproof • Leakproof

Medihaler-EPI®

Epinephrine bitartrate, 7.0 mg. per cc., suspended in inert, nontoxic aerosol vehicle. Contains no alcohol. Each measured dose contains 0.15 mg. epinephrine.

Medihaler-ISO®

Isoproterenol sulfate, 2.0 mg. per cc., suspended in inert, nontoxic aerosol vehicle. Contains no alcohol. Each measured dose contains 0.06 mg. isoproterenol.

NOTABLY SAFE AND EFFECTIVE FOR CHILDREN, TOO.

Riker

Northridge, California

AN AMES CLINIQUICK™

CLINICAL BRIEFS FOR MODERN PRACTICE

Why is the three-day biliary flush recommended after cholecystectomy?

To remove stones and debris frequently present in the common duct when choledochostomy has not been done.

Source: Best, R. R.; Rasmussen, J. A., and Wilson, C. E.: A.M.A. Arch. Surg. *67*:839, 1953.

THREE-DAY BILIARY FLUSH*

BEFORE BREAKFAST	6 oz. Citrate of Magnesia
AFTER BREAKFAST	3 **DECHOLIN with Belladonna** tablets
BEFORE LUNCH	3 tablespoons pure cream or olive oil
AFTER LUNCH	3 **DECHOLIN with Belladonna** tablets
BEFORE SUPPER	3 tablespoons pure cream or olive oil 1 nitroglycerin tablet (1/100 gr.) under the tongue
AFTER SUPPER	3 **DECHOLIN with Belladonna** tablets
AT BEDTIME	3 **DECHOLIN with Belladonna** tablets

*Adapted from Best, R. R., and others: ibid.

for hydrocholeresis plus reliable spasmolysis

DECHOLIN® WITH BELLADONNA

(dehydrocholic acid with belladonna, AMES)

in postoperative management—"Hydrocholeretic therapy is employed as a routine feature... in patients with cholecystectomy, cholecystostomy, and other biliary tract procedures."[1]

in medical management—"... also recommended for patients with a clinical history of biliary tract disease when gallbladder disease has not been confirmed."[2]

1. Refresher Article: M. Times *85*:1081 (Oct.) 1957.
2. Best, R. R.: Mod. Med. *25*:264 (March 15) 1957.

for hydrocholeresis

DECHOLIN®

(dehydrocholic acid, AMES)

Available: DECHOLIN/Belladonna tablets (dehydrocholic acid, AMES) 3¾ gr. (250 mg.) and extract of belladonna ⅙ gr. (10 mg.) Bottles of 100 and 500.

DECHOLIN tablets: (dehydrocholic acid, AMES) 3¾ gr. (250 mg.) Bottles of 100, 500, and 1,000; drums of 5,000.

AMES
COMPANY, INC
Elkhart • Indiana
Toronto • Canada

71289

in your hospitalized patient

Compazine* offers

4 beneficial effects

- relieves anxiety and tension
- controls nausea
- stops postoperative vomiting
- eases emotional stress that may aggravate pain and other psychosomatic symptoms

Also, hypotension is minimal and infrequent—a particular advantage in surgical patients.

For immediate effect: Ampuls and Multiple dose vials.
Also available: Tablets, Spansule† sustained release capsules, Suppositories and Syrup.

SKF SMITH KLINE & FRENCH LABORATORIES

*T.M. Reg. U.S. Pat. Off. for prochlorperazine, S.K.F.
†T.M. Reg. U.S. Pat. Off.

COVER THE
SUMMER FRONT...
WITH THREE
HIGHLY EFFECTIVE
CORTICOSTEROID
TOPICALS

INFLAMMATORY AND ALLERGIC SKIN CONDITIONS

Aristocort® *CREAM*

Triamcinolone Acetonide 0.1%
TUBES OF 5 GM. AND 15 GM.

Aristocort® *OINTMENT*

Triamcinolone Acetonide 0.1%
TUBES OF 5 GM. AND 15 GM.

INFLAMMATORY, ALLERGIC, INFECTIVE EYE AND EAR CONDITIONS

Neo-Aristocort®

Neomycin-Triamcinolone Acetonide 0.1%
TUBES OF ⅛ OZ.

EYE-EAR OINTMENT

Each...sparingly applied...offers the unique efficacy of ARISTOCORT in topical situations...with 10-fold the potency of hydrocortisone topically yet *without* the hazards associated with systemic absorption

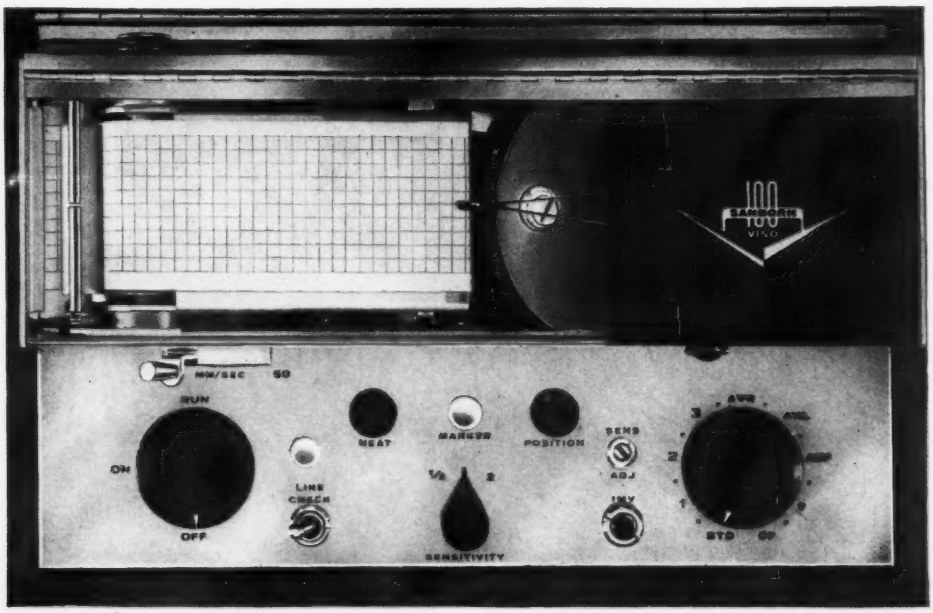
Lederle

LEDERLE LABORATORIES, A Division of AMERICAN CYANAMID COMPANY, Pearl River, New York

The new Sanborn 100 Viso electrocardiograph: two speeds . . . 25 or 50 mm/sec . . . clearly defined, permanent traces on 6cm charts . . . normal, ½, or 2-times recording sensitivity . . . two additional inputs for recording other phenomena, plus outlet for connecting monitoring oscilloscope . . . 15 transistors saving space, weight, and power . . . and the mobility of 29 pounds, complete . . . make this

FUNCTIONALLY AND FACTUALLY

the most modern electrocardiograph you can own



EIGHT-HUNDRED FIFTY DOLLARS DELIVERED CONTINENTAL U.S.A. • • SANBORN COMPANY • WALTHAM, MASS.

NIATRIC™

TABLETS AND ELIXIR

To add life to years—not merely years to life . . . Niatric sharpens mental acuity and promotes a return to more normal social and physical activity for your aged patients.

In the Old Age Syndrome . . . Niatric relieves confusion, forgetfulness, irritability, depression and apathy—the penalties of advancing age.

- **Niatric improves respiration and cerebral function**
- **Niatric improves circulation**
- **Niatric protects capillary integrity**
- **Niatric prevents brain tissue hypoxia**

Niatric contains:	Each Tablet:	5 cc. Elixir:
Pentylenetetrazol	100 mg.	100 mg.
Nicotinic Acid	50 mg.	50 mg.
Ascorbic Acid	100 mg.	100 mg.
Bioflavonoids	100 mg.	-----
Alcohol	-----	15%

Average Dose: 1 tablet or 1 tsp. (5 cc.) t.i.d.
Supply: Tablets, bottles of 100 and 500.
Elixir, bottles of 1 pint.

Send now for samples and literature . . .

B. F. ASCHER AND COMPANY, INC.

Ethical Medicinals / Kansas City, Missouri

there's pain and inflammation here... it could be mild or severe, acute or chronic, primary or secondary fibrositis—or even early rheumatoid arthritis

more potent and comprehensive treatment than salicylate alone

. . . assured anti-inflammatory effect of low-dosage corticosteroid[1]

. . . additive antirheumatic action of corticosteroid plus salicylate[2-5] brings rapid pain relief; aids restoration of function.

. . . wide range of application including the entire fibrositis syndrome as well as early or mild rheumatoid arthritis

more manageable corticosteroid dosage

. . . much less likelihood of treatment-interrupting side effects[1-6]

. . . simple, flexible dosage schedule

in any case
it calls for

Sigmagen®

corticoid-salicylate compound

tablets

Acute conditions: Two or three tablets four times daily. After desired response is obtained, gradually reduce daily dosage and then discontinue.

Subacute or chronic conditions: Initially as above. When satisfactory control is obtained, gradually reduce the daily dosage to minimum effective maintenance level. For best results administer after meals and at bedtime.

Precautions: Because SIGMAGEN contains prednisone, the same precautions and contraindications observed with this steroid apply also to the use of SIGMAGEN.

Composition

METICORTEN® (prednisone)	0.75 mg.
Acetylsalicylic acid	325 mg.
Aluminum hydroxide	75 mg.
Ascorbic acid	20 mg.

Packaging: SIGMAGEN Tablets, bottles of 100 and 1000.

References: 1. Spies, T. D., et al.: J.A.M.A. 159:645, 1955. 2. Spies, T. D., et al.: Postgrad. Med. 17:1, 1955. 3. Gelli, G., and Della Santa, L.: Minerva Pediat. 7:1456, 1955. 4. Guerra, F.: Fed. Proc. 12:326, 1953. 5. Busse, E. A.: Clin. Med. 2:1105, 1955. 6. Sticker, R. B.: Panel Discussion, Ohio State M. J. 52:1037, 1956.

SCHERING CORPORATION • BLOOMFIELD, N. J.

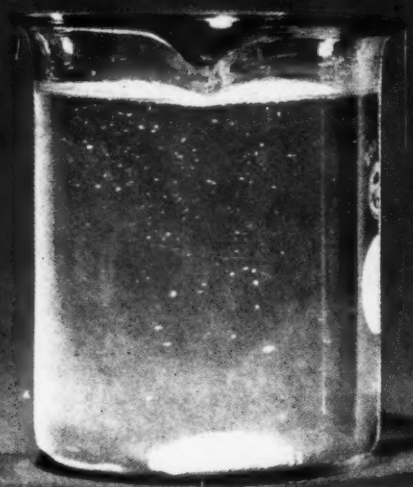
80-J-648

Schering

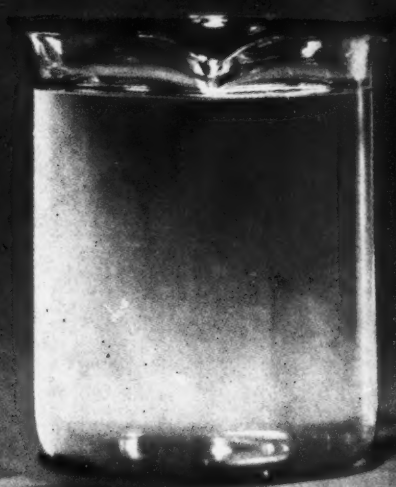
avoid the risk of insoluble, irritating aspirin particles

Chief among the drawbacks to aspirin usage is gastric intolerance. This ranges from mild upset and "heartburn" to severe hemorrhagic gastritis.[1-3] Studies performed in conjunction with gastrectomy[4-6] and gastroscopy[4] have shown insoluble aspirin particles firmly adherent to the gastric mucosa and imbedded between rugae. Reactions varying from mild hyperemia to erosive gastritis have been reported to occur in the areas immediately surrounding these adherent particles.[7-9] This is reported to be particularly true in patients with peptic ulcer.[7]

CALURIN is the freely soluble, stable calcium aspirin complex. Its high solubility forestalls gastric irritation or damage.



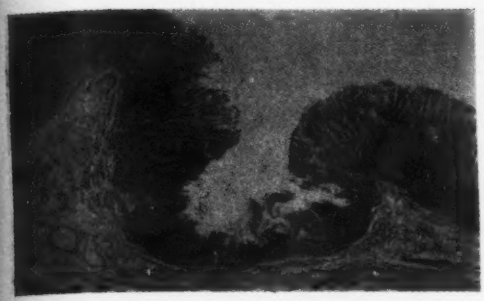
Regular aspirin crystals 24 hours after being mixed into water.



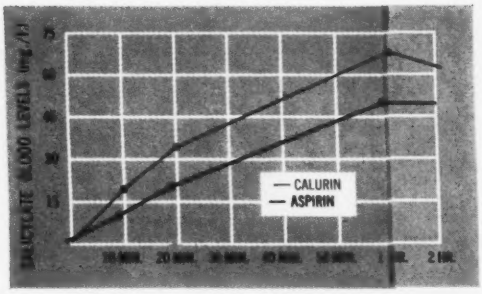
Calurin crystals in solution one minute after being mixed into water.

CALURIN*

STABLE SOLUBLE CALCIUM-ACETYLSALICYLATE-CARBAMIDE



Particle-induced ulceration — section through lesion found in gastrectomy specimen. An aspirin particle was found firmly imbedded in this undermined erosion. Such lesions may be associated with the relative insolubility of aspirin, which remains in particulate form after dispersion in gastric contents.



Calurin, being freely soluble, is promptly available for absorption into the systemic circulation. Salicylate blood levels in 12 subjects receiving both Calurin and plain aspirin were found to rise more than twice as high within ten minutes following Calurin. Also, these levels persisted higher for at least two hours.[11]

CALURIN is the aspirin of choice, especially when high-dosage, long-term therapy is indicated:

1 High solubility forestalls gastric irritation or damage. This advantage is of special importance in arthritis and other conditions requiring high-dosage, long-term therapy.

2 Produces high salicylate blood levels rapidly for prompt analgesic, anti-pyretic, anti-arthritic effect.

3 Sodium-free — for safer long-term therapy.

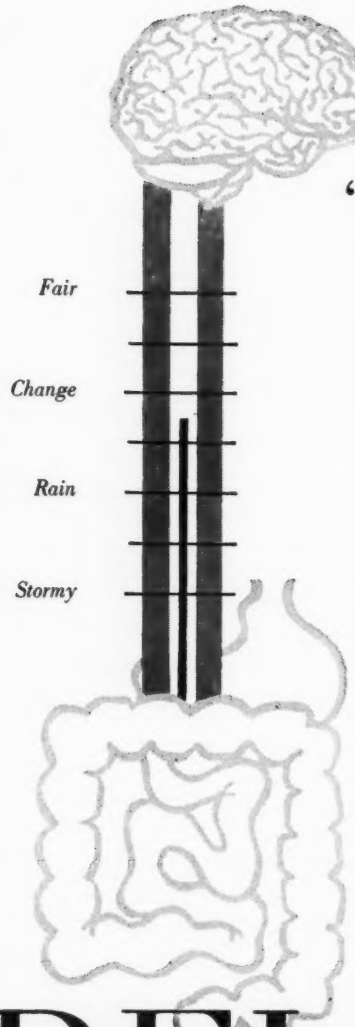
4 Flavored: can be chewed or dissolved in the mouth without water if desired — an advantage for patients requiring aspirin administration during the night and for pediatric patients.

Dosage: Each tablet of Calurin is equivalent to 300 mg. (5 gr.) of acetylsalicylic acid. For relief of pain and fever in adult patients, the usual dose of Calurin is 1 to 3 tablets every 4 hours, as needed; in arthritic states, 2 or 3 tablets 3 or 4 times daily; in rheumatic fever, 3 to 5 tablets 4 or 5 times daily. For children over 6 years, the usual dose is 1 tablet every 4 hours; for children 3 to 6 years, ½ tablet every 4 hours, as required. Not recommended for children under 3.

REFERENCES: 1. Waterson, A. P.: Aspirin and gastric haemorrhage, Brit. M. J. **2**:1531, 1955. 2. Douthwaite, A. H., and Lintott, G. A. M.: Gastroscopic observation of the effect of aspirin and certain other substances on the stomach, Lancet **2**:1222, 1938. 3. Editorial Comments: The effect of acetylsalicylic acid (aspirin) on the gastric mucosa, Canad. M. A. J. **80**:47, 1959. 4. Muir, A., and Cossar, I. A.: Aspirin and ulcer, Brit. M. J. **2**:7, 1955. 5. Muir, A., and Cossar, I. A.: Aspirin and gastric haemorrhage, Lancet **1**:539, 1959. 6. Schneider, E. M.: Aspirin as a gastric irritant, Gastroenterology **33**:616, 1957. 7. Bayles, T. B., and Tenckhoff, H.: Salicylate therapy in rheumatic diseases, Scientific Exhibit, Ann. Mtg. A. M. A., San Francisco, Calif., June, 1958. 8. Batterman, R. C.: Comparison of buffered and unbuffered acetylsalicylic acid, New Eng. J. M. **258**:213, 1958. 9. Cronk, G. A.: Laboratory and clinical studies with buffered and nonbuffered acetylsalicylic acid, New Eng. J. M. **258**:219, 1958. 10. Editorial: Aspirin plain and buffered, Brit. M. J. **1**:349, 1959. 11. Smith, P. K.: Plasma concentration of salicylate after the administration of acetylsalicylic acid or calcium acetylsalicylate to human subjects, Report submitted to Smith-Dorsey from Dept. of Pharmacology, Geo. Washington Univ. School of Medicine, Washington, D. C., Sept. 5, 1958.

*TRADEMARK

SMITH-DORSEY• a division of The Wander Company • Lincoln, Nebraska



"the G-I tract is the barometer of the mind..."

Belbarb soothes the agitated mind and calms the G-I spasm through the central effect of phenobarbital and the synergistic action of fixed proportions of natural belladonna alkaloids on the gastrointestinal tract.

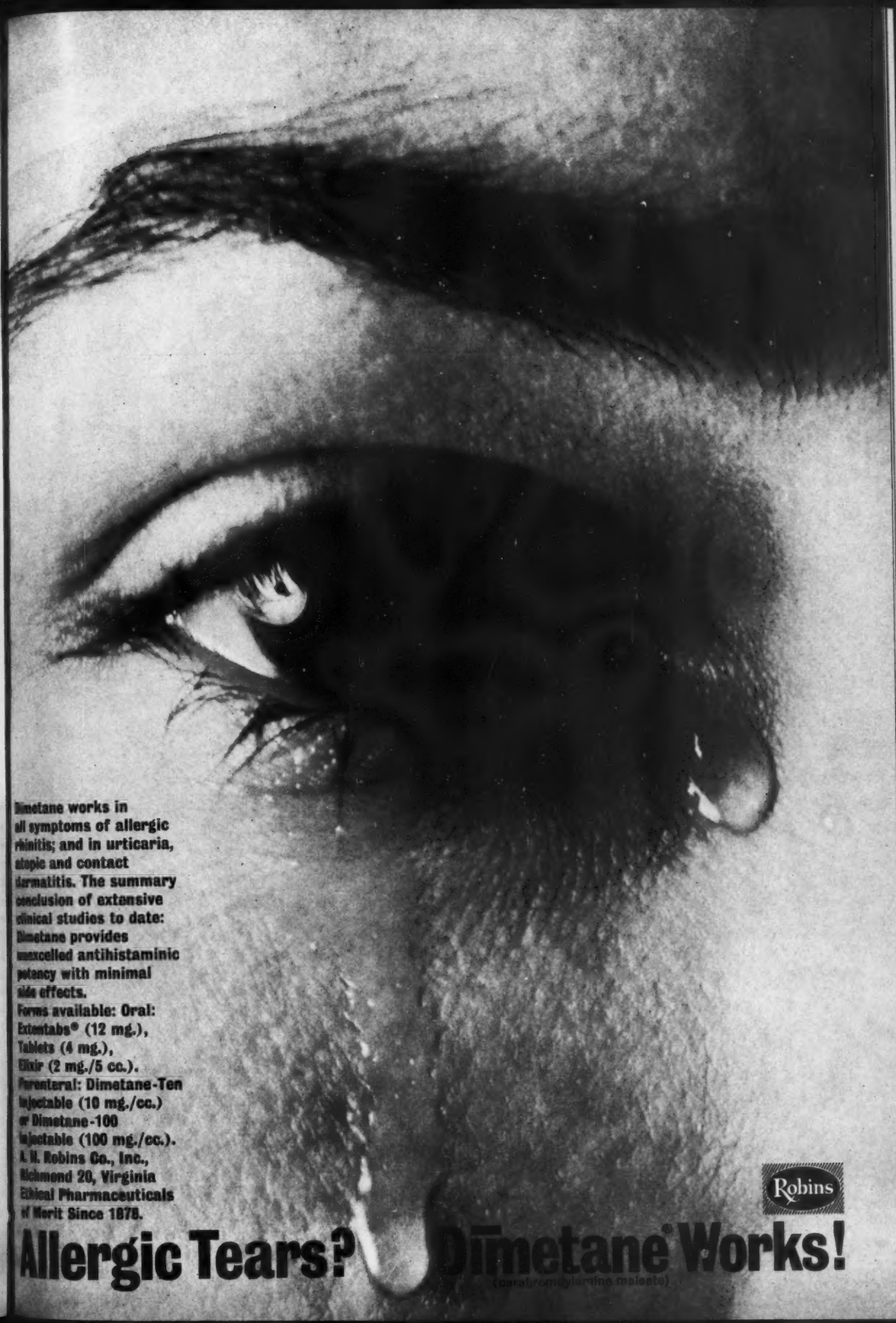
BELBARB

SEDATIVE ANTISPASMODIC

20 years of clinical satisfaction

Belbarb No. 1; Belbarb No. 2; Belbarb Elixir; Belbarb-B; Belbarb Trisules

CHARLES C. HASKELL *& COMPANY, Richmond, Virginia*


Dimetane works in all symptoms of allergic rhinitis; and in urticaria, atopic and contact dermatitis. The summary conclusion of extensive clinical studies to date: Dimetane provides unexcelled antihistaminic potency with minimal side effects.
Forms available: Oral: Extentabs® (12 mg.), Tablets (4 mg.), Elixir (2 mg./5 cc.). Parenteral: Dimetane-Ten Injectable (10 mg./cc.) or Dimetane-100 Injectable (100 mg./cc.).
A. H. Robins Co., Inc., Richmond 20, Virginia
Ethical Pharmaceuticals of Merit Since 1878.
Robins
Allergic Tears?
Dimetane® Works!
(parabromdylamine maleate)

Clinical findings in 900 patients show the selective antihypertensive action of Singoserp

IN 735 PATIENTS, BLOOD PRESSURE FELL AN AVERAGE OF 30.7 mm. Hg:

- more than half of these patients suffered from **moderate to severe hypertension**
- more than half of the cases involved hypertension of at least 6 years' standing, with **many histories of up to 20 years' duration**

THE SIDE-EFFECTS PROBLEM WAS MINIMIZED IN MOST PATIENTS:

Chart shows gratifyingly low incidence of side effects in 233 patients given Singoserp with no other antihypertensive medication

Side Effect	Number	Per Cent
Lethargy	7	2.9
Headache	6	2.5
Gastrointestinal upset	3	1.2
Vertigo	2	0.8
Nasal congestion	1	0.4

DOSAGE: Initially, 1 to 2 tablets (1 to 2 mg.) daily.
SUPPLIED: Singoserp *Tablets*, 1 mg. (white, scored); bottles of 100.
Samples available on request. Write to CIBA, Box 277, Summit, N.J.

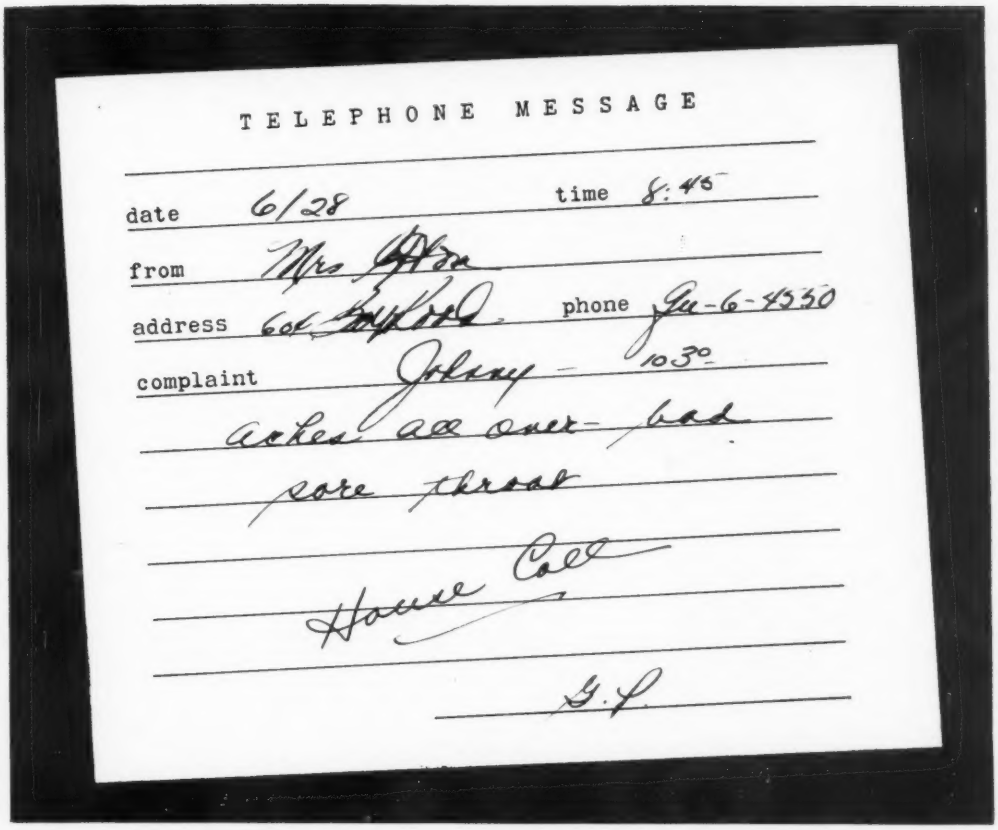
Singoserp®
(syrosingopine CIBA)

CIBA
SUMMIT, N.J.

remember
Serpasil®
(reserpine CIBA)
for the anxious hypertensive with or without tachycardia

a major improvement in rauwolfia

a major advance in antihypertensive therapy



the house-call antibiotic

COSA-SIGNEMYCIN®

glucosamine-potentiated tetracycline with triacetyloleandomycin

wide range of action is reassuring when culture and sensitivity tests are impractical

More than 90 clinical references attest to the superiority and effectiveness of Cosa-Signemycin (Signemycin). Bibliography and professional information booklet available on request.

CAPSULES: *125 mg., 250 mg.*

ORAL SUSPENSION: *raspberry flavored, 2 oz. bottle, 125 mg. per teaspoonful (5 cc.)*

PEDIATRIC DROPS: *raspberry flavored, 10 cc. bottle (with calibrated dropper) 5 mg. per drop (100 mg. per cc.)*

Pfizer *Science for the world's well-being*

PFIZER LABORATORIES
Division, Chas. Pfizer & Co., Inc.
Brooklyn 6, N. Y.

the disease of many masks

Doctor, do you recognize this patient? She complains of flatulence, constipation with alternating periods of diarrhea, and colicky pains in the lower right quadrant. At other times she is troubled by anorexia, lassitude, dull headache, muscle pains and backache. Or she may have only one or two of these symptoms.

In these puzzling cases, serious consideration should be given to intestinal amebiasis—the disease of many masks. Clinicians say it is "one of the most widespread and serious protozoan diseases of man," yet "there is no parasite more often misdiagnosed than is *E. histolytica*." Conservative estimates place the incidence at 10% of the United States population as a whole, and 16% in southern states.

Now Glarubin, a relatively non-toxic amebicide, simplifies the treatment of suspected cases of intestinal amebiasis. Glarubin, a crystalline glycoside from the fruit of *Simarouba glauca*, is a specific amebicidal agent with minimal side effects. It contains no arsenic, bismuth or iodine.

Glarubin is administered orally in tablet form and does not require strict medical supervision or hospitalization. Extensive clinical trials prove it highly effective in intestinal amebiasis, and virtually free of toxicity.

Supplied in bottles of 40 tablets, each tablet containing 50 mg. of glaucarubin. Write for descriptive literature, bibliography, and dosage schedules.

new Glarubin

TABLETS

specific for intestinal amebiasis

THE S. E. MASSENGILL COMPANY

BRISTOL, TENNESSEE

NEW YORK • KANSAS CITY • SAN FRANCISCO

Remarkable
relief from
low back pain and
dysmenorrhea
Trancopal
THE FIRST TRUE TRANQUILAXANT

Here i
can expec
prescrib

case profile no. 2758*

for low back pain fo

A middle-aged man had intermittent low back pain attributed to injuries received in an automobile accident three years ago. The pain radiated down both legs, making the patient walk bent over. He also had difficulty in getting out of bed and had to pull his knees up and roll out. Any heavy lifting precipitated a new attack, and he tired easily.

Findings on x-ray of the thoracic and lumbar spine were negative. All other laboratory studies were within normal limits. A herniated disc, though still a possibility, was temporarily ruled out by the neurologic examination. Previous treatment consisted of analgesics, steroids (without success), and narcotics during severe attacks.

On a dosage of Trancopal, 100 mg. t.i.d., this patient is able to walk around almost normally and carry on his regular activities as long as he does not overdo. He has received Trancopal for over seven months with excellent relief of symptoms. There have been no side effects.

**Clinical Reports on file at the Department of Medical Research, Winthrop Laboratories.*

e i what you
ec when you
ib

THE FIRST TRUE TRANQUILAXANT

Trancopal®

pain for dysmenorrhea
and premenstrual tension

case profile no. 3347*

A 35-year-old housewife had a history of severe dysmenorrhea and premenstrual tension. Menarche occurred at the age of 14. She is a gravida 2, para 1. Her menstrual cycle is fairly regular, and previous medical history indicates no apparent abnormalities. Findings on pelvic examination were negative. Severe tension and irritability routinely occurred from two to seven days before and during menstruation. Cramping was experienced for all three days of the menstrual period. Analgesic preparations provided limited symptomatic relief.

Trancopal, 200 mg. t.i.d., was prescribed for dysmenorrhea. It not only has relieved the severe cramping, but has provided a welcome relief from the irritability accompanying it. Because of these excellent results, Trancopal also was prescribed for her tenseness during the premenstrual period with a most gratifying response.

This patient has successfully remained on the above regimen for over six months without adverse effects.

Turn Page for Complete Listing of Indications and Dosage

THE FIRST TRUE TRANQUILAXANT

Trancopal

potent muscle relaxant

effective tranquilizer

- In musculoskeletal disorders, effective in 91% of patients.[1]
- In anxiety and tension states, effective in 88% of patients.[1]
- Low incidence of side effects (2.3% of patients). Blood pressure, pulse rate, respiration and digestive processes unaffected by therapeutic dosage. No effects on hematopoietic system or liver and kidney function.
- No gastric irritation. Can be taken before meals.
- No clouding of consciousness, no euphoria or depression.

Indications:

Musculoskeletal:
Low back pain (lumbago, etc.)
Neck pain (torticollis, etc.)
Bursitis
Rheumatoid arthritis
Osteoarthritis
Disc syndrome
Fibrositis
Ankle sprain, tennis elbow, etc.
Myositis
Postoperative muscle spasm

Psychogenic:
Anxiety and tension states
Dysmenorrhea
Premenstrual tension
Asthma
Angina pectoris
Alcoholism

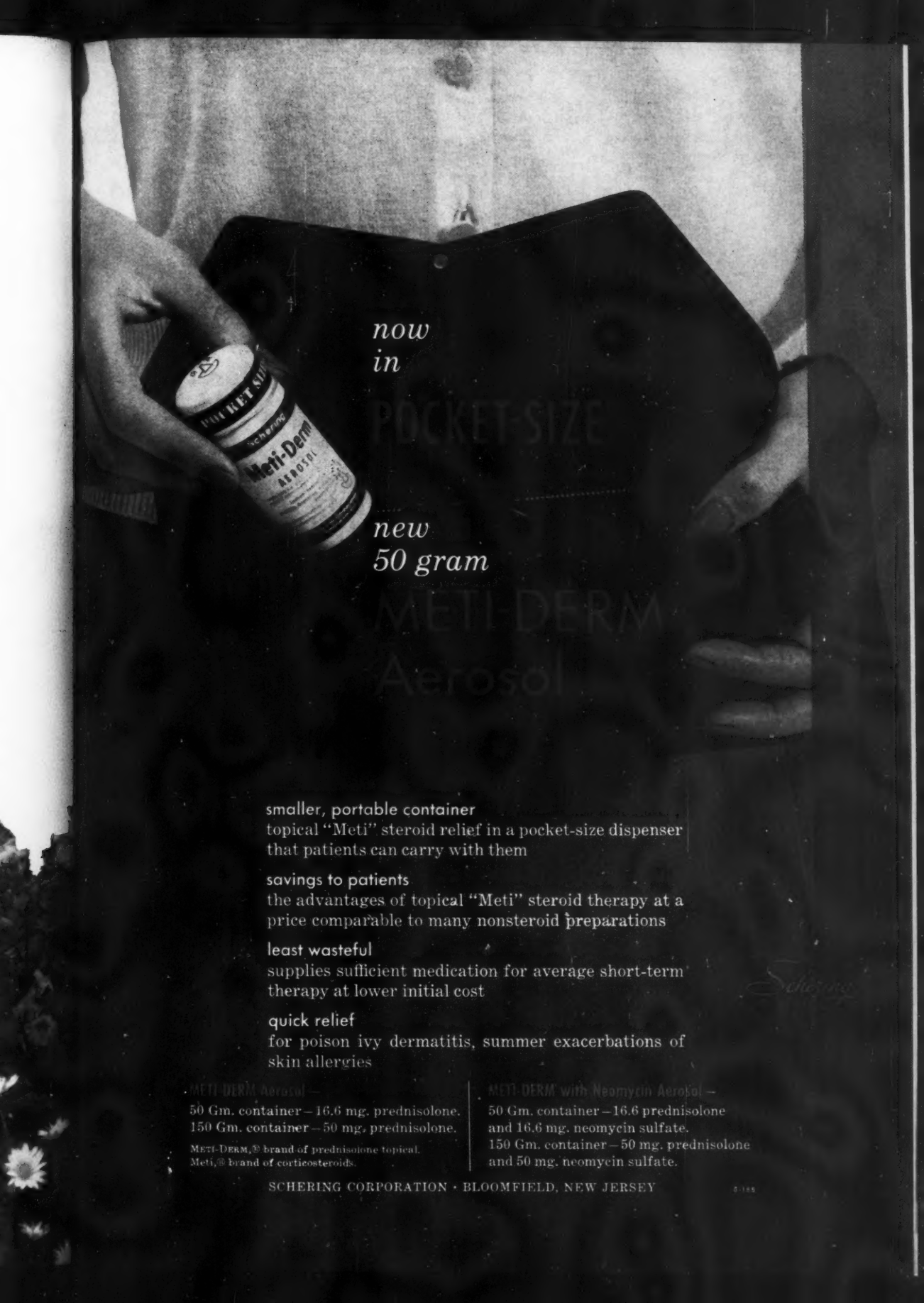
Trancopal Caplets®:
100 mg. (peach colored, scored), bottles of 100.

Dosage: Adults, 100 or 200 mg. orally three or four times daily. Relief of symptoms occurs in fifteen to thirty minutes and lasts from four to six hours.

1. Collective Study, Department of Medical Research, Winthrop Laboratories.

Winthrop LABORATORIES
New York 18, New York

Trancopal (brand of chlormezanone) and Caplets, trademarks reg. U.S Pat. Off. Printed in U.S.A. 6-59 (1385M)



smaller, portable container
topical "Meti" steroid relief in a pocket-size dispenser that patients can carry with them

savings to patients
the advantages of topical "Meti" steroid therapy at a price comparable to many nonsteroid preparations

least wasteful
supplies sufficient medication for average short-term therapy at lower initial cost

quick relief
for poison ivy dermatitis, summer exacerbations of skin allergies

METI-DERM Aerosol—
50 Gm. container—16.6 mg. prednisolone.
150 Gm. container—50 mg. prednisolone.

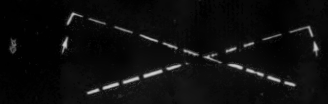
METI-DERM with Neomycin Aerosol—
50 Gm. container—16.6 prednisolone and 16.6 mg. neomycin sulfate.
150 Gm. container—50 mg. prednisolone and 50 mg. neomycin sulfate.

METI-DERM,® brand of prednisolone topical.
Meti,® brand of corticosteroids.

SCHERING CORPORATION · BLOOMFIELD, NEW JERSEY

probably the easiest-to-use x-ray table in its field

Instant swing through from fluoroscopy to radiography (and vice versa). Self guiding to correct operating distance. Nothing to match up . . . you do it without leaving the table front.



Horizontal, vertical, intermediate, or Trendelenburg positions by equipoise handrock (or quiet motor-drive).

Choice of rotating or stationary anode x-ray tubes. Full powered 100 ma at 100 KVP.

certainly the simplest automatic x-ray control ever devised

know why? *look . . .*

1. On this board you select the bodypart you want to x-ray
2. Set its measured thickness
3. Press the exposure button

That's all there is to it. No time, KV, or MA adjusting to do. No charts to check, no calculations to make.

housed in this handsome upright cabinet

obviously as canny an x-ray investment as you can make

Modest cost
Excellent value
Prestige "look"
Top Reputation (significantly, "Century" trade-in value has long been highest in its field)

And you can rent if you prefer.

Call in your Picker representative (he's probably in your local 'phone book) or write: PICKER X-RAY CORPORATION 25 South Broadway, White Plains, N. Y.

anatomatic Century
diagnostic x-ray unit

x-ray

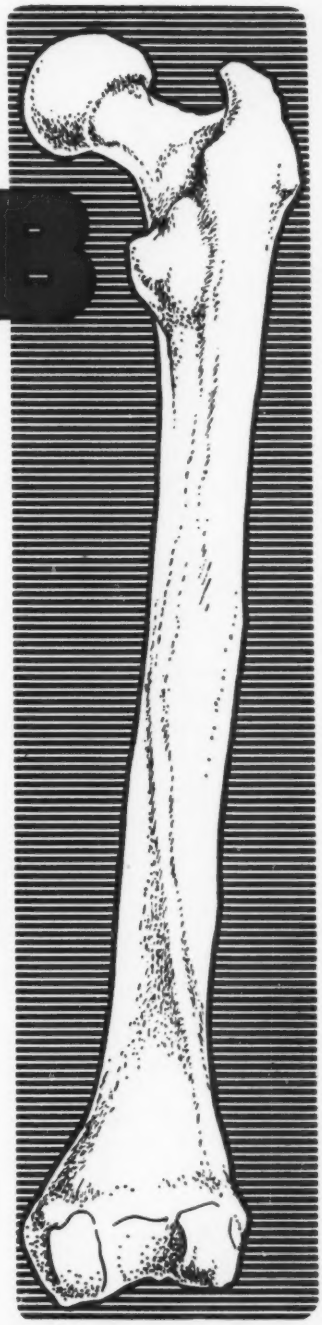
for bone health

prescribe

CAL-O-B

TABLETS, W-T

because calcium glycerophosphate provides uniquely assimilable calcium and phosphorus.



• Cal-O-B calcium produces greater calcium deposition in bone than other commonly used phosphated or phosphorus-free calcium compounds. It is completely soluble and assimilable throughout the entire pH range of the G.I. tract. Cal-O-B Tablets also supply vitamins D, B_6 and C with iron and 12 trace minerals.

Each Tablet Contains:

Calcium Glycerophosphate	500 mg.
Ferrous Gluconate	200 mg.
Vitamin D_2 (Calciferol)	1000 units
Pyridoxine Hydrochloride	1 mg.
Ascorbic Acid	50 mg.
Twelve Trace Minerals	7.83 mg.

WARREN-TEED PHARMACEUTICALS

THE WARREN-TEED PRODUCTS COMPANY

COLUMBUS 8, OHIO

Dallas Chattanooga Los Angeles Portland

what to do about RUNS...
eye RUNS...
nose RUNS...

patient "blue" and listless

in allergy

NALERTAN

a new Neisler Durabond® product

dries secretions

eliminates congestion

stops itching

brightens the outlook

all day or night with a single oral dose . . . with a remarkable lack of side effects

DURABOND

in pollen allergies, contact dermatoses, food sensitivities, and a wide variety of allergic associated disorders

NALERTAN provides

new chemical forms of two outstanding antihistamines . . . acting synergistically for broad, prolonged blockage of histamine response.

a long-acting sympathomimetic . . . to lift the misery, combat lassitude and brighten the outlook . . . hasten recovery.

Employs the Durabond principle . . . to act within minutes . . . relieves for hours . . . just one dose in the morning controls lacrimation, makes breathing easier, relieves itching—all day. And, one dose upon retiring keeps the patient symptom-free . . . allows uninterrupted rest all night.

1 or 2 tablets twice a day. For economy, prescribe in original pkgs. of 100.

Each Durabond tabule contains: Chlorpheniramine tannate, 8 mg.; Pyrilamine tannate, 25 mg.; Tanphetamin (*d*-amphetamine tannate), 10 mg.

Neisler **IRWIN, NEISLER & CO.**
DECATUR, ILLINOIS

IT HAPPENS IN THE BEST | NOURISHED OF FAMILIES

VITERRA®

meets the specific vitamin-mineral needs of every member of the household — select the form that suits the age and condition of each patient best

VITERRA CAPSULES — comprehensive daily supplement. Bottles of 100.

VITERRA TASTITABS®—can be chewed, dissolved, or swallowed. Bottles of 100.

VITERRA THERAPEUTIC—high potency formula. Bottles of 30 and 100.

VITERRA PEDIATRIC—for infants and small children. 50 cc. Metered-Flow bottle.

Selectively formulated by one of the major producers of bulk vitamins

ROERIG Rx

New York 17, N. Y.
Division, Chas. Pfizer & Co., Inc.
Science for the World's Well-Being

Novahistine works better than antihistamines alone

Stuffy, runny noses... swollen, weepy eyes are more effectively relieved with Novahistine. The distinctly additive action of the vasoconstrictor and antihistamine combined in Novahistine relieves allergic symptoms more effectively than either drug alone.

one dose of 2 tablets for day-long or night-long relief. Each long-acting tablet contains Phenylephrine HCl 20 mg. and Chlorprophenpyridamine maleate 4 mg. Bottles of 50 and 250 green, film-coated tablets.

PITMAN-MOORE COMPANY Division of Allied Laboratories, Inc., Indianapolis 6, Indiana

Novahistine LP* LONG-ACTING

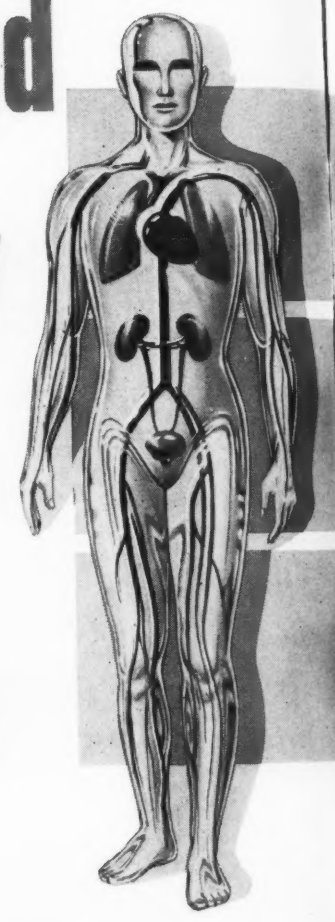
*Trademark

NEW

HYDRODIURIL®

(HYDROCHLOROTHIAZIDE)

simplifies* and improves any regimen for hypertension



*it

*it's as easy as 1, 2, 3 to use

HYDRODIURIL

(HYDROCHLOROTHIAZIDE)

1 Initiate therapy with HYDRODIURIL: one 25 mg. tablet or one 50 mg. tablet once or twice a day. HYDRODIURIL by itself often causes an adequate drop in blood pressure over a period of two to three weeks. This may be all the therapy some patients require.

2 Add or adjust other agents as required: HYDRODIURIL enhances the activity of all commonly-used antihypertensive agents; thus, the dosage of other medication (rauwolfia, reserpine, hydralazine, veratrum) should be initiated or adjusted as indicated by patient condition. If a ganglion-blocking agent is contemplated or being used, usual dosage must be reduced by 50 per cent.

3 Adjust dosage of all medication: the patient must be frequently observed and careful adjustment of all agents should be made to establish optimal maintenance dosage.

Supplied: 25 mg. and 50 mg scored tablets HYDRODIURIL (Hydrochlorothiazide) bottles of 100 and 1,000.
Additional literature for the physician is available on request.

HYDRODIURIL is a trademark of Merck & Co., INC. Trademarks outside the U. S.: DICHLOTRIDE, DICLOTRIDE, HYDROSALURIC.

MSD MERCK SHARP & DOHME, Division of Merck & Co., INC., Philadelphia 1, Pa.

Against the "Vaginitis Spectrum"

TRICHOMONAS
MONILIA
BACTERIA

A welcome clinical advance...
effective medication
in an appealing form

Soft and pliant as a tampon, the Milibis vaginal suppository offers proved therapeutic action* in a vehicle giving unusual clinical advantages to both patients and physician.

COVERS CERVIX AND VAGINAL WALL—The pliant Milibis suppository disintegrates readily and molds itself to the cervix as well as the columns and rugae of the vaginal vault.

SHORT DOSAGE SCHEDULE—The short course of treatment with Milibis—only 10 suppositories in most cases—together with the clean, odorless, non-staining qualities eliminates psychic barriers which often interrupt longer treatments before complete cure.

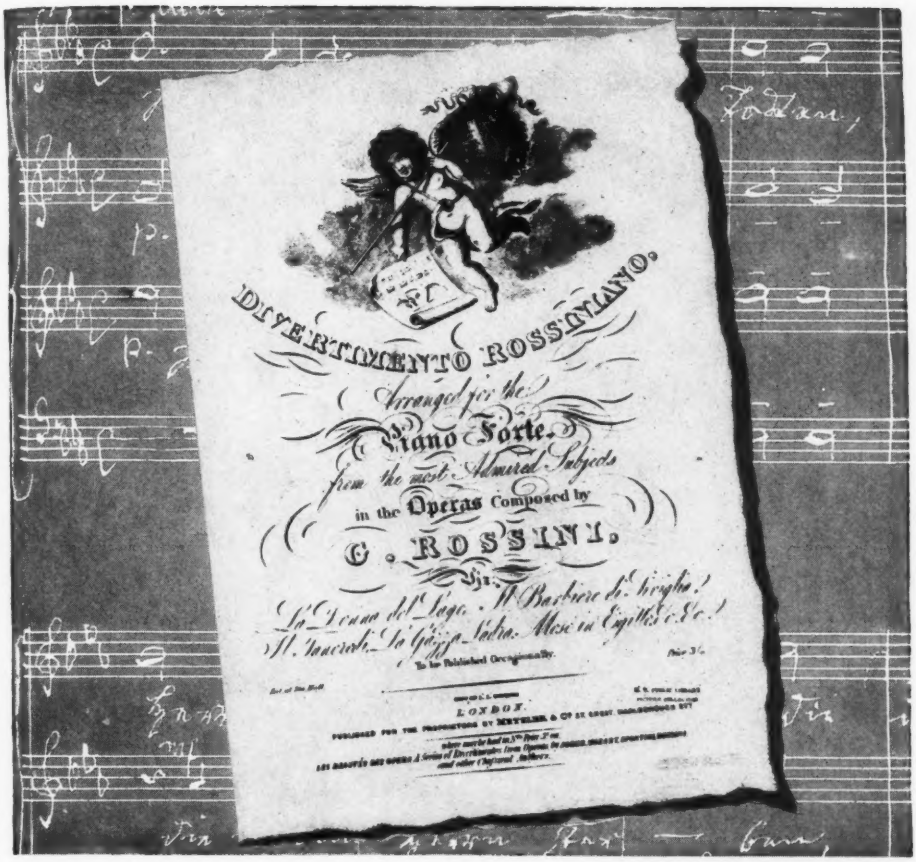
SUPPLIED: BOXES OF 10 with applicator.

Now supplied with plastic applicator
- SANITARY
- INSURES CORRECT SUPPOSITORY PLACEMENT

MILIBIS® Vaginal Suppositories

Winthrop LABORATORIES
New York 18, N.Y.

*97 per cent effective in a study of 564 cases; 94 per cent effective in a series of 510 cases.

Milibis (brand of glycobiarsol), trademark reg. U.S. Pat. Off.

The great operatic works of Rossini have been enjoyed by millions for many decades

THINGS THAT ENDURE

Good things endure . . . a work of art, a literary classic, a proud bridge . . . a dependable pharmaceutical. Such is **Desitin Ointment.** For over 35 years Desitin Ointment has endured as an incomparable, safe way to prevent and clear up diaper rash . . . and as a soothing, healing application in wounds, burns, external ulcers and other skin injuries.

Desitin®

DESITIN CHEMICAL COMPANY PROVIDENCE 4, R. I.

Regularity and Metamucil

Both are basic for relief and correction of constipation

Effective relief and correction of constipation require more than clearing the bowel. Basic to the actual correction of the condition itself is the establishment of regular bowel habits. Equally basic is Metamucil which adds a soft, inert bulk to the bowel contents to stimulate normal peristalsis and also to retain water within stools to keep them soft and easy to pass. Thus Metamucil induces natural elimination and promotes regularity.

Metamucil®
brand of psyllium hydrophilic mucilloid

SEARLE

RHINALL NOSE DROPS

For quick, effective relief of nasal congestion

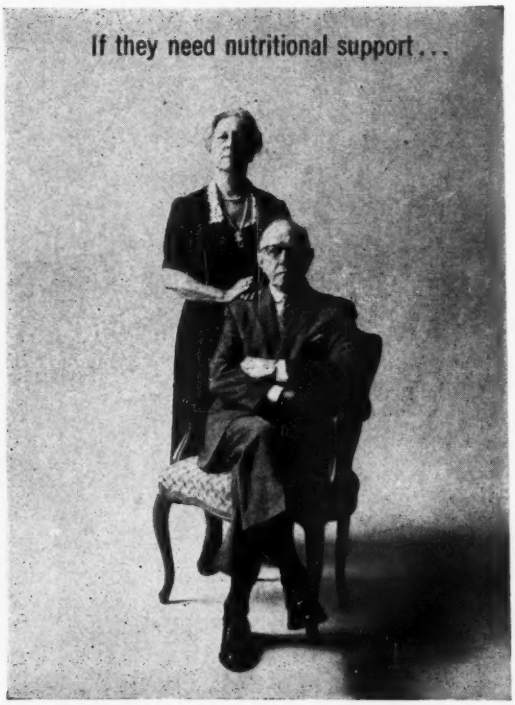
Safe for both children and adults, Rhinall Nose Drops are pleasant to use, provide ventilation and drainage without irritation of the ciliated epithelium.

no burning or irritation • no risk of sensitization
no bad taste or after reactions

SUPPLIED: one-ounce dropper bottle: ½-ounce plastic spray bottle.

RHINOPTO COMPANY
3905 Cedar Springs
Dallas, Texas

Contains:
Phenylephrine Hydrochloride 0.15%
"Propadrine" Hydrochloride 0.3%
in an isotonic saline menstruum



they deserve

GEVRAL®

Vitamin-Mineral Supplement Lederle

CAPSULES—14 VITAMINS—11 MINERALS

LEDERLE LABORATORIES, a Division of
AMERICAN CYANAMID COMPANY, Pearl River, New York

Lederle

general use...
in general practice

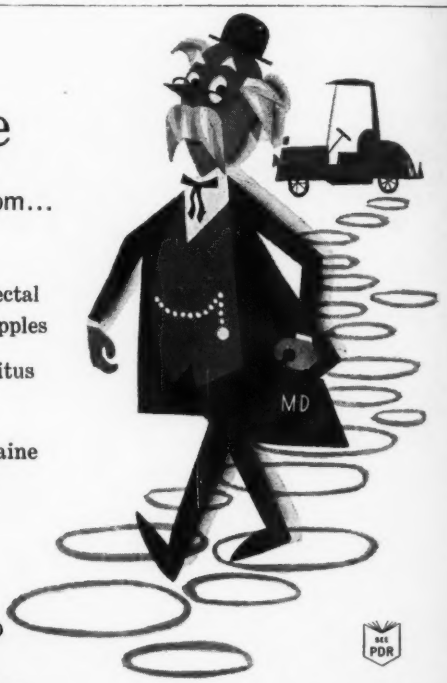
fast, effective and long-lasting relief from...

BURNS – sunburn, cooking, ironing

PAIN – hemorrhoids and inoperable anorectal conditions, cuts and abrasions, cracked nipples

ITCHING – insect bites, poison ivy, pruritus

The water-soluble, nonstaining base melts on contact with the tissue, releasing the Xylocaine for immediate anesthetic action. It does not interfere with the healing processes.



Astra Pharmaceutical Products, Inc.,
Worcester 6, Mass., U.S.A.

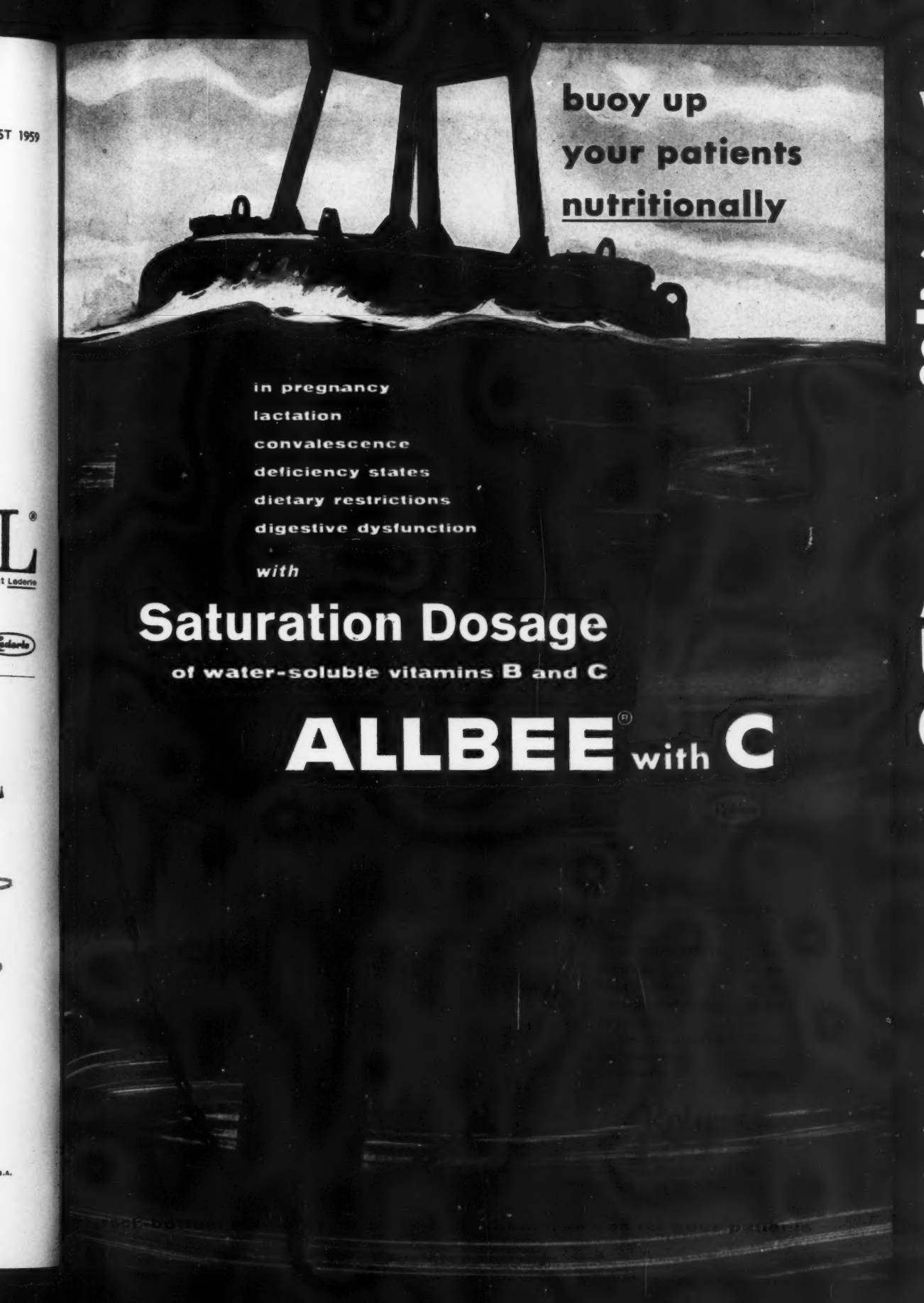
XYLOCAINE®

(brand of lidocaine*)

OINTMENT 2.5% & 5%

SEE PDR

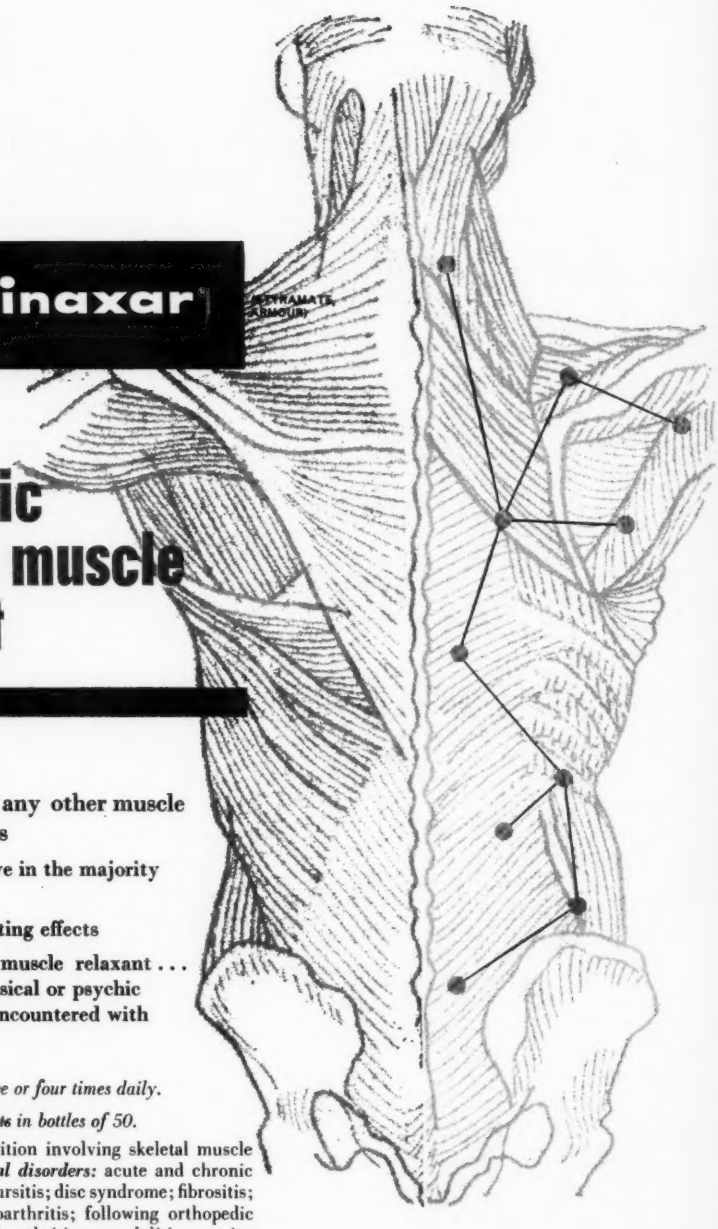
*U.S. PAT. NO. 2,441,498 MADE IN U.S.A.


buoy up
your patients
nutritionally
in pregnancy
lactation
convalescence
deficiency states
dietary restrictions
digestive dysfunction
with
Saturation Dosage
of water-soluble vitamins B and C
ALLBEE® with C

rely on

Sinaxar

METHAMATE (ARMOUR)



a specific skeletal muscle relaxant

Chemically unlike any other muscle relaxant, Sinaxar is

- **consistently effective in the majority of cases**
- **long acting: no fleeting effects**
- **purely a skeletal muscle relaxant . . . free of adverse physical or psychic effects frequently encountered with tranquilizers**

DOSAGE: *Two tablets three or four times daily.*

SUPPLIED: *200 mg. tablets in bottles of 50.*

INDICATIONS: Any condition involving skeletal muscle spasm, as ***musculoskeletal disorders:*** acute and chronic back ache; arthritides; bursitis; disc syndrome; fibrositis; myalgia; myositis; osteoarthritis; following orthopedic procedures; rheumatoid arthritis; spondylitis; sprains and strains; torticollis; ***neurologic disorders:*** cerebral palsy; cerebrovascular accidents; cervical root syndrome: multiple sclerosis.

ARMOUR

ARMOUR PHARMACEUTICAL COMPANY • *A Leader in Biochemical Research* • KANKAKEE, ILLINOIS

THE **BUFFERED**
ACID VAGINAL DOUCHE
BUFFERED
TO **MAINTAIN**
AN ACID pH*

Mildly astringent soothing inflamed tissue

•

Low surface tension effectively penetrating vaginal folds

•

"Clean" refreshing odor assuring patient acceptance

•

Valuable adjunct in management of monilia, trichomonas, staphylococcus and streptococcus vaginal infections.

*See reverse side for detail.

MASSENGILL® POWDER

THE S M GILL COMP
Cit

pH

massengill® powder

The **BUFFERED**
acid vaginal douche

What is a BUFFER?

Medical dictionaries define it as a substance which, added to a solution, causes resistance to any change of hydrogen-ion concentration (pH) when either acid or alkali is added.

Significance of buffers in Massengill Powder

The normal vagina has a pH of 3 to 4.5. This low pH inhibits growth of most pathogenic invaders. Usually, an infection will cause the pH to rise to the neutral or alkaline range which favors the multiplication of pathogens.

The alkaline mucosa neutralizes a simple, unbuffered acid douche, like vinegar, within 30 minutes.

In contrast, the *buffered* acid douche solution of Massengill Powder (pH 3.5–4.5) resists neutralizing. The normal, low pH is maintained for 4 to 6 hours and as long as 24 hours in recumbent patients. This low pH inhibits the propagation of monilia, trichomonas vaginalis and pathogenic bacteria. However, the beneficial Döderlein bacillus thrives in this pH range.

THE S. E. MASSENGILL COMPANY

Bristol, Tennessee • New York • Kansas City • San Francisco

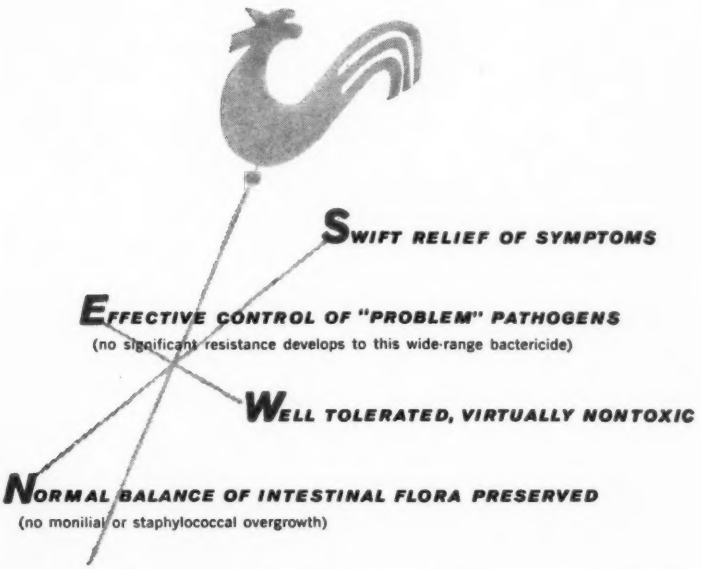
TO STOP DIARRHEA

from all points... growing evidence favors

FUROXONE®

brand of furazolidone

▪ Pleasant-flavored LIQUID, 50 mg. per 15 cc. (with kaolin and pectin) ▪ Convenient TABLETS, 100 mg. ▪ Dosage—400 mg. daily for adults, 5 mg./Kg. daily for children (in 4 divided doses).


SWIFT RELIEF OF SYMPTOMS
EFFECTIVE CONTROL OF "PROBLEM" PATHOGENS
(no significant resistance develops to this wide-range bactericide)
WELL TOLERATED, VIRTUALLY NONTOXIC
NORMAL BALANCE OF INTESTINAL FLORA PRESERVED
(no monilial or staphylococcal overgrowth)

From a Large Midwestern University: FUROXONE Controls Antibiotic-Resistant Outbreak. An outbreak of bacillary dysentery due to Shigella sonnei was successfully controlled with FUROXONE after a broad-spectrum antibiotic had proved inadequate. Cure rates (verified by stool culture) were 87% with FUROXONE, 36% with chloramphenicol. Only FUROXONE "failures" were those lost to follow-up. Chloramphenicol failures subsequently treated with FUROXONE responded without exception. FUROXONE was also used effectively as prophylaxis and to eliminate the carrier state. It was "extremely well tolerated in all 191 individuals who received it either prophylactically or therapeutically."

Galeota, W.R., and Moranville., B.A.: Student Medicine (in press)

THE NITROFURANS—A UNIQUE CLASS OF ANTIMICROBIALS EATON LABORATORIES, NORWICH, NEW YORK

Fostex®
treats their acne while they wash

degreases the skin helps remove blackheads dries and peels the skin

...and this is how it works

Fostex provides essential actions necessary in treating acne. It washes off excess oil. It unblocks pores by penetrating and softening blackheads. It dries and peels the skin, removing papule coverings, thus permitting drainage of sebaceous glands.

Fostex contains Sebulytic®,* a combination of surface-active wetting agents with remarkable antiseborrheic, keratolytic and antibacterial actions . . . enhanced by sulfur 2%, salicylic acid 2%, hexachlorophene 1%.

*sodium lauryl sulfoacetate, sodium alkyl aryl polyether sulfonate and sodium dioctyl sulfosuccinate.

Your patients will like Fostex because it is so simple to use. They simply wash acne skin 2 to 4 times a day with Fostex, instead of using soap.

FOSTEX CREAM

. . . in 4.5 oz. jars. For therapeutic washing in the initial phase of oily acne treatment.

Write for samples.

FOSTEX CAKE

. . . in bar form. For therapeutic washing to keep the skin dry and free of blackheads during maintenance therapy. Also used in relatively less oily acne.

WESTWOOD PHARMACEUTICALS Buffalo 13, New York

NEW

isoclor

provides both . . . / upper respiratory decongestion and bronchial decongestion

Many hay fever patients also experience chest discomfort. For these patients, new ISOCLOR provides relief along the entire respiratory tract.

COMBINES the nasal and bronchial decongestant action of d-isoephedrine with the histamine blocking action of chlorpheniramine.

RELIEVES the discomforts of rhinorrhea, itching, sneezing, hyperlacrimation and post nasal drip— the patient get a full night's rest—with minimal daytime drowsiness, CNS or pressor stimulation.

TABLETS AND SYRUP for adults and children . . .

COMPOSITION:	Per tablet	Per 5 ml. syrup
Chlorpheniramine maleate	4 mg.	2 mg.
d-Isoephedrine HCl	25 mg.	12.5 mg.

DOSE: Tablets: One tablet 3 or 4 times daily. Syrup: Children: 3-6 yrs. ½ tsp. t.i.d.; 6-12 yrs. 1 tsp. t.i.d.; Adults: 2 tsp. t.i.d.

AVAILABLE: Tablets: Bottles of 100. Syrup: Pint bottles.

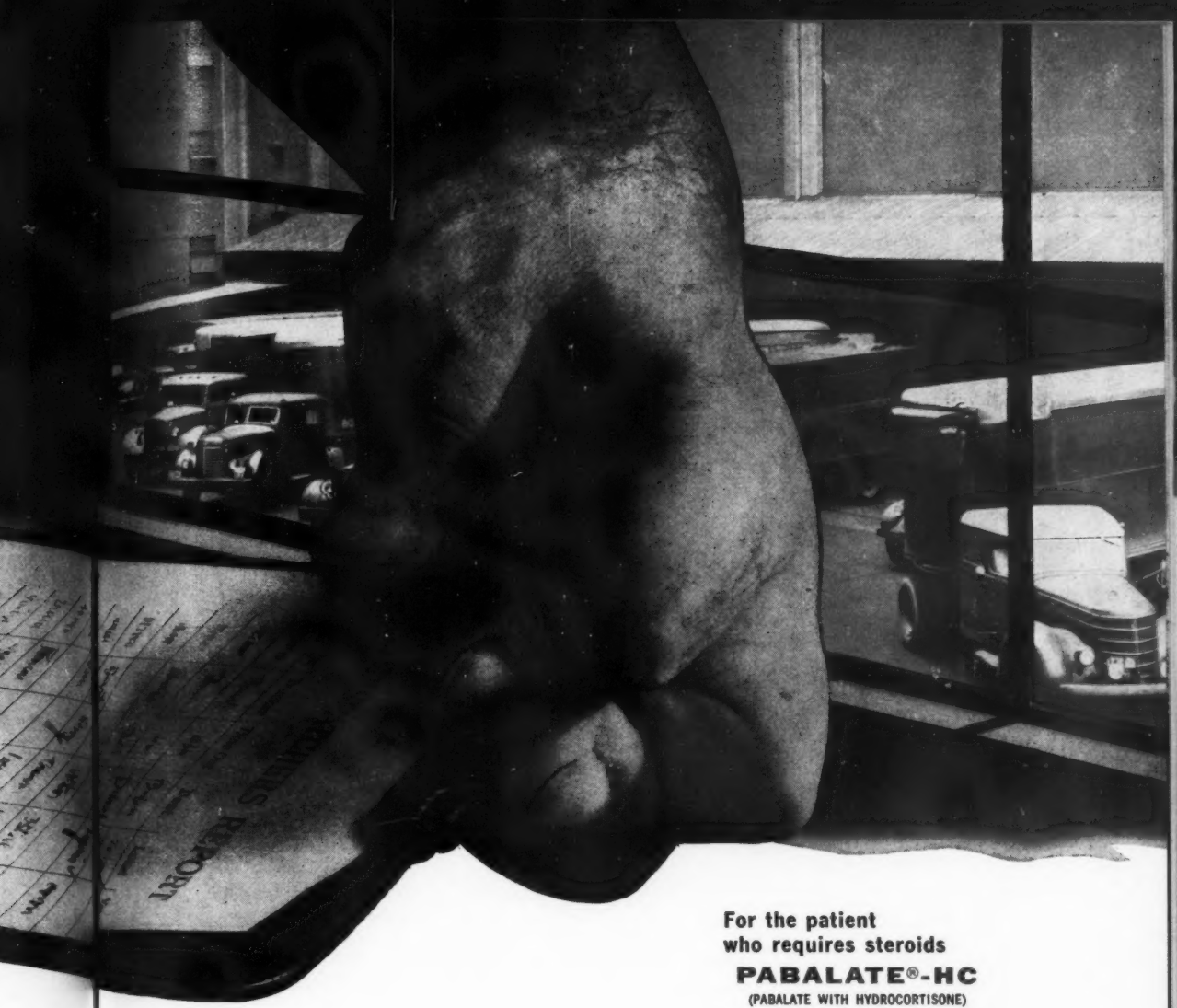
CHARLES C.
HASKELL
& COMPANY
Richmond, Virginia

Your difficult rheumatic patient . . .

on the job again

through effective relief and rehabilitation

Robins



For the patient who does not require steroids

PABALATE®

Reciprocally acting nonsteroid antirheumatics . . . more effective than salicylate alone.

In each enteric-coated tablet:

Sodium salicylate U.S.P.....0.3 Gm. (5 gr.)
Sodium para-aminobenzoate .....0.3 Gm. (5 gr.)
Ascorbic acid .....50.0 mg.

or for the patient who should avoid sodium

PABALATE®-Sodium Free

Pabalate, with sodium salts replaced by potassium salts.

In each enteric-coated tablet:

Potassium salicylate .....0.3 Gm. (5 gr.)
Potassium para-aminobenzoate .....0.3 Gm. (5 gr.)
Ascorbic acid .....50.0 mg.

For the patient who requires steroids

PABALATE®-HC

(PABALATE WITH HYDROCORTISONE)

Comprehensive synergistic combination of steroid and nonsteroid antirheumatics... full hormone effects on low hormone dosage . . . satisfactory remission of rheumatic symptoms in 85% of patients tested.

In each enteric-coated tablet:

Hydrocortisone (alcohol) ..... 2.5 mg.
Potassium salicylate ..... 0.3 Gm.
Potassium para-aminobenzoate.. 0.3 Gm.
Ascorbic acid .....50.0 mg.

PABALATE® Robins PABALATE®-HC

For steroid or non-steroid therapy: SAFE DEPENDABLE ECONOMICAL

A. H. ROBINS CO., INC., RICHMOND 20, VIRGINIA • Ethical Pharmaceuticals of Merit since 1878

Established Standard Therapy in Hypertension*

Rauwiloid

alseroxylon, 2 mg.

*Because

Rauwiloid provides effective Rauwolfia action virtually free from side effects... the smooth therapeutic efficacy of Rauwiloid is associated with significantly less toxicity than reserpine... and with a lower incidence of depression. Tolerance does not develop.

Rauwiloid is initial therapy for every hypertensive patient. ...Dosage adjustment is never a problem...

just two tablets at bedtime

After full effect one tablet suffices

When more potent drugs are needed, prescribe one of the *convenient single-tablet combinations*

alseroxylon 1 mg. and alkavervir 3 mg.

or

alseroxylon 1 mg. and hexamethonium chloride dihydrate 250 mg.

Many patients with severe hypertension can be maintained on Rauwiloid alone after desired blood pressure levels are reached with combination medication.

Riker

Northridge, California

even if your patient is a - mud chicken†

†surveyor, to non-engineers

he won't be mired for long once he's on

PARAFON*

PARAFLEX® + TYLENOL®

for muscle relaxation *plus* analgesia

prescribe PARAFON in low back pain – sprains – strains – rheumatic pains

Each PARAFON tablet contains: PARAFLEX® Chlorzoxazone† . . 125 mg. Specific for skeletal muscle spasm TYLENOL® Acetaminophen . . 300 mg. The analgesic preferred in musculoskeletal pain

Supplied: Tablets, scored, pink, bottles of 50.

Dosage: Two tablets three or four times a day.

and in arthritis

PARAFON* with Prednisolone

Each PARAFON WITH PREDNISOLONE tablet contains: PARAFLEX® Chlorzoxazone† 125 mg., TYLENOL® Acetaminophen 300 mg., and prednisolone 1.0 mg.

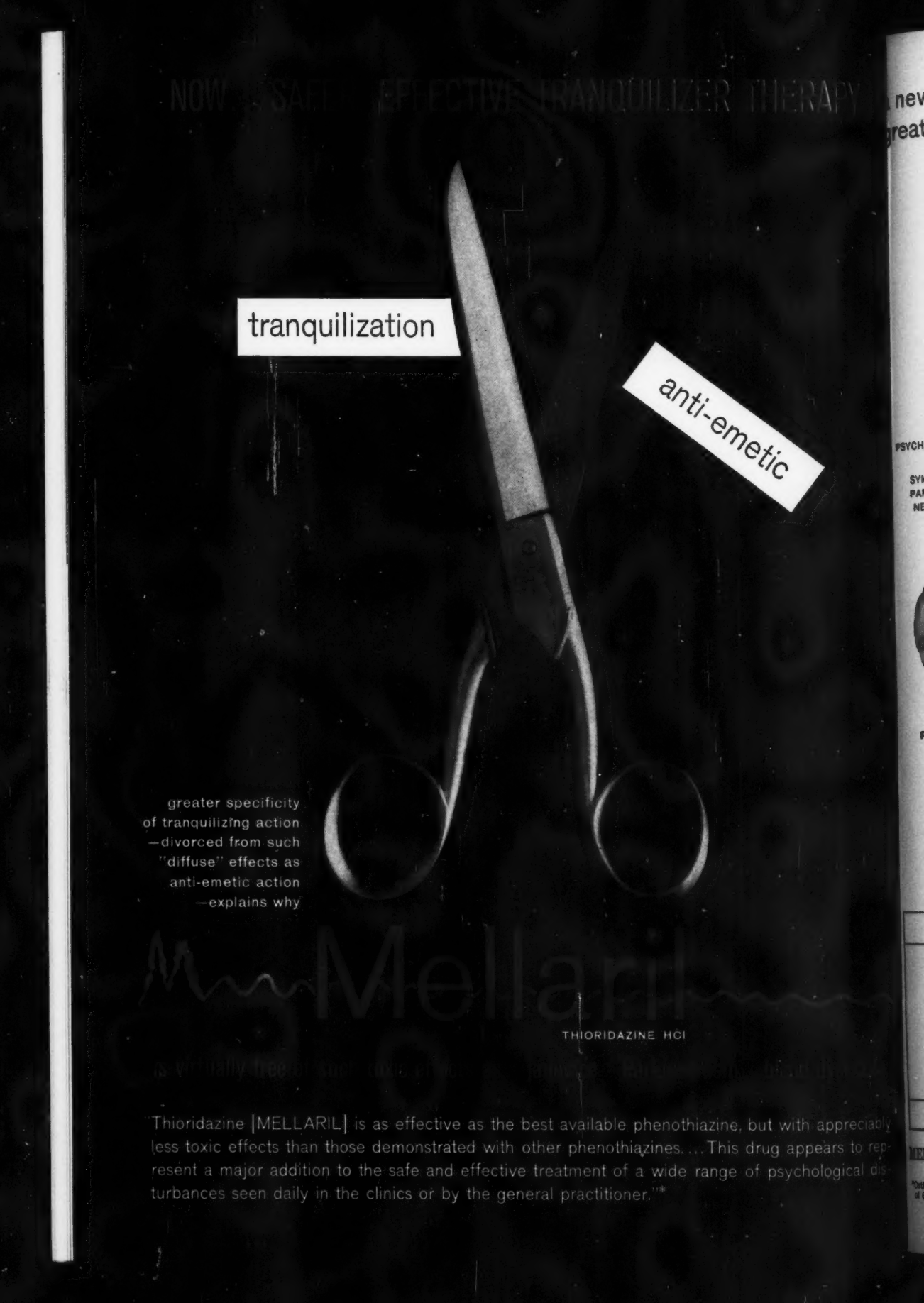
Supplied: Tablets, scored, buff colored, bottles of 36.

Dosage: One to two tablets three or four times a day.

Precautions: The precautions and contraindications that apply to all steroids should be kept in mind when prescribing PARAFON WITH PREDNISOLONE.

*Trade-mark †U. S. Patent Pending

McNeil Laboratories, Inc • Philadelphia 32, Pa.



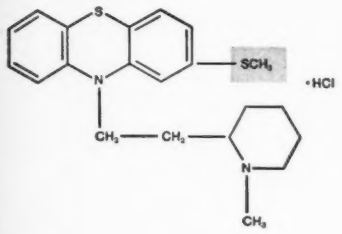
greater specificity
of tranquilizing action
—divorced from such
"diffuse" effects as
anti-emetic action
—explains why

Mellaril

THIORIDAZINE HCl

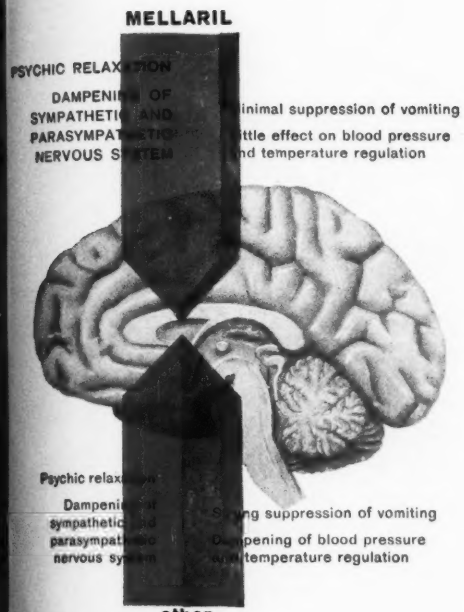
Thioridazine [MELLARIL] is as effective as the best available phenothiazine, but with appreciably less toxic effects than those demonstrated with other phenothiazines. ... This drug appears to represent a major addition to the safe and effective treatment of a wide range of psychological disturbances seen daily in the clinics or by the general practitioner."*

new advance in tranquilization:
greater specificity of tranquilizing action results in fewer side effects



The presence of a thiomethyl radical (S-CH_3) is unique in Mellaril and could be responsible for the relative absence of side effects and greater specificity of psychotherapeutic action. This is shown clinically by:

1 A specificity of action on certain brain sites in contrast to the more generalized or "diffuse" action of other phenothiazines. This is evidenced by a lack of appreciable anti-emetic effect.



2 Less "spill-over" action to other brain areas — hence, absence of undue sedation, drowsiness or autonomic nervous system disturbances.

3 A notable absence of extrapyramidal stimulation.

4 Lack of impairment of patient's normal drive and energy.

5 Virtual freedom from such toxic effects as jaundice, photosensitivity, skin eruptions, blood forming disorders.

INDICATION	USUAL STARTING DOSE	TOTAL DAILY DOSAGE RANGE
ADULTS: Mental and Emotional Disturbances:		
MILD—where anxiety, apprehension and tension are present	10 mg. t.i.d.	20-60 mg.
MODERATE—where agitation exists in psychoneuroses, alcoholism, intractable pain, senility, etc.	25 mg. t.i.d.	50-200 mg.
SEVERE—in agitated psychotic states as schizophrenia, manic depressive, toxic psychoses, etc.:		
Ambulatory	100 mg. t.i.d.	200-400 mg.
Hospitalized	100 mg. t.i.d.	200-800 mg.
CHILDREN: BEHAVIOR PROBLEMS IN CHILDREN	10 mg. t.i.d.	20-40 mg.

MELLARIL Tablets, 10 mg., 25 mg., 100 mg.

[illegible], A. M.: Scientific Exhibit, American Academy of General Practice, San Francisco, April 6-9, 1959.

SANDOZ

In response to innumerable requests from dermatologists

Winthrop Laboratories now makes available

TRIQUIN®

FOR LUPUS ERYTHEMATOSUS AND LIGHT-SENSITIVITY ERUPTIONS

WHAT IT IS:

A combination of Atabrine® hydrochloride 25 mg., Aralen® phosphate 65 mg. and Plaquenil® sulfate 50 mg.

WHAT IT'S FOR:

Treatment of lupus erythematosus (chronic discoid type) and polymorphic light eruptions (light-sensitivity eruptions, solar urticaria or dermatitis).

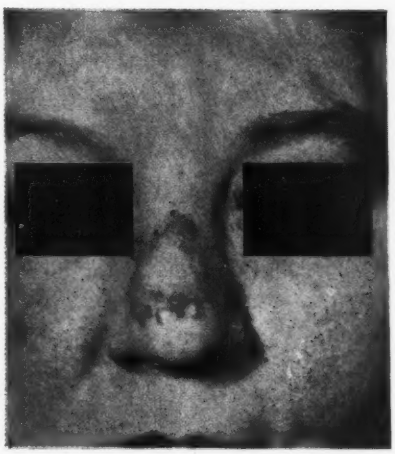
HOW IT ACTS:

Each of the three components produces beneficial response in lupus erythematosus and light-sensitivity eruptions. Since the dose of each of the Triquin components is very low, overall toxicity is reduced and clinical tolerance improved. Furthermore, the three components appear to act synergistically.

HOW SUPPLIED:

Triquin tablets in bottles of 100, sold on prescription only.

Write for TRIQUIN booklet.



DOSAGE:

Lupus. Average initial adult dose, 1 or 2 tablets after meals and at bedtime. Dosage should be reduced gradually at two week intervals to 1 or 2 daily.

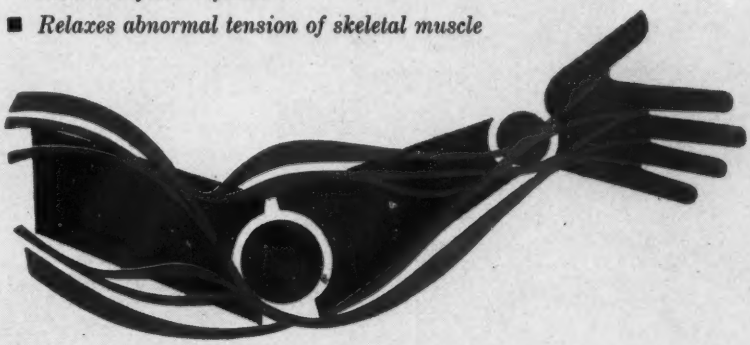
Light-Sensitivity Eruptions. Average initial adult dose, 1 tablet after breakfast and lunch. May be reduced after several weeks to maintenance dosage of 1 tablet daily.

Triquin, Atabrine (brand of quinacrine), Aralen (brand of chloroquine), and Plaquenil (brand of hydroxychloroquine), trademarks reg. U.S. Pat. Off.

Winthrop LABORATORIES New York 18, N. Y.

now... a new way to relieve pain and stiffness in muscles and joints

- *Exhibits unusual analgesic properties, different from those of any other drug*
- *Specific and superior for relief of* SOMAtic *pain*
- *Modifies central perception of pain without abolishing natural defense reflexes*
- *Relaxes abnormal tension of skeletal muscle*



SOMA™

N-isopropyl-2-methyl-2-propyl-1, 3-propanediol dicarbamate

In back pain, bursitis, sprains, strains, and bruises, whiplash and other traumatic injuries, inflammatory and degenerative muscle and joint complaints.

RAPID ACTING. Pain-relieving and relaxant effects start within 30 minutes and last for at least 6 hours.

NOTABLY SAFE. Toxicity is extremely low. No effects on liver, endocrine system, blood pressure, blood picture or urine have been reported. Some patients may become sleepy on higher than recommended dosage.

EASY TO USE. Usual adult dose is one 350 mg. tablet 3 times daily and at bedtime.

SUPPLIED: Bottles of 50 white sugar-coated 350 mg. tablets.

Literature and samples on request.

WALLACE LABORATORIES, NEW BRUNSWICK, N. J.

BIBLIOGRAPHY

1. J. Pharm. & Exp. Ther. 89:131
2. J. Urology 73:487
3. J. Mo. Med. Assoc. 48:685
4. Med. Rec. & Annals 43:1104

IN G. I. OR G. U. SPASM

Thioethylamine (-$SCH_2CH_2N<$), nucleus of the Trocinate molecule, is common to enzymes involved in the contraction of smooth muscle cells. Sulfur, the key atom of the thioethylamine group, is also basic to the chemistry of muscle contractions, entering into the essential reversible oxidation-reduction reactions. These identities suggest that the strong, direct inhibiting action of Trocinate upon muscle-cell contraction, independent of general suppression of the parasympathetic nervous system, is that of a true anti-metabolite. Skeletal muscles are not affected.

Comprehensively evaluated pharmacologically[1] and clinically[2,3,4], Trocinate is a potent and dependable antispasmodic, yet is remarkably free from side-effects, and will not cause mydriasis, anuria, or tachycardia. Its antisialogogue effect is extremely low.

Dosage: **The basic adult dosage is two Trocinate tablets, three or four times daily, but dosage may be safely increased in severe spasm.**

Wm. P. Poythress *& Co., Inc.*

RICHMOND 17, VIRGINIA

The menopausal patient in need of psychic support . . . the postpartum patient suffering the "baby blues" . . . the convalescent patient worried about her future health . . . these and many other patients will often benefit from the antidepressant, mood-lifting effect of

Dexamyl® Tablets • Elixir
Spansule® brand of sustained release capsules

brand of dextro amphetamine plus amobarbital

When the depressed patient is particularly listless and lethargic, she will often benefit from the gentle stimulating effect of

Dexedrine® Tablets • Elixir • Spansule® capsules
brand of dextro amphetamine

Smith Kline & French Laboratories

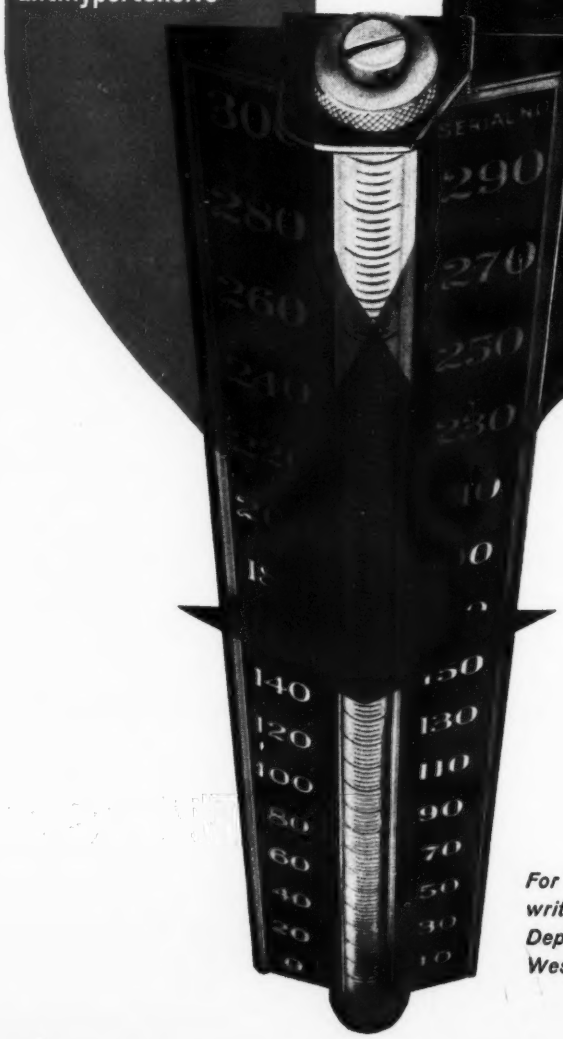
greater antihypertensive effect...fewer side effect

HYDROPRES

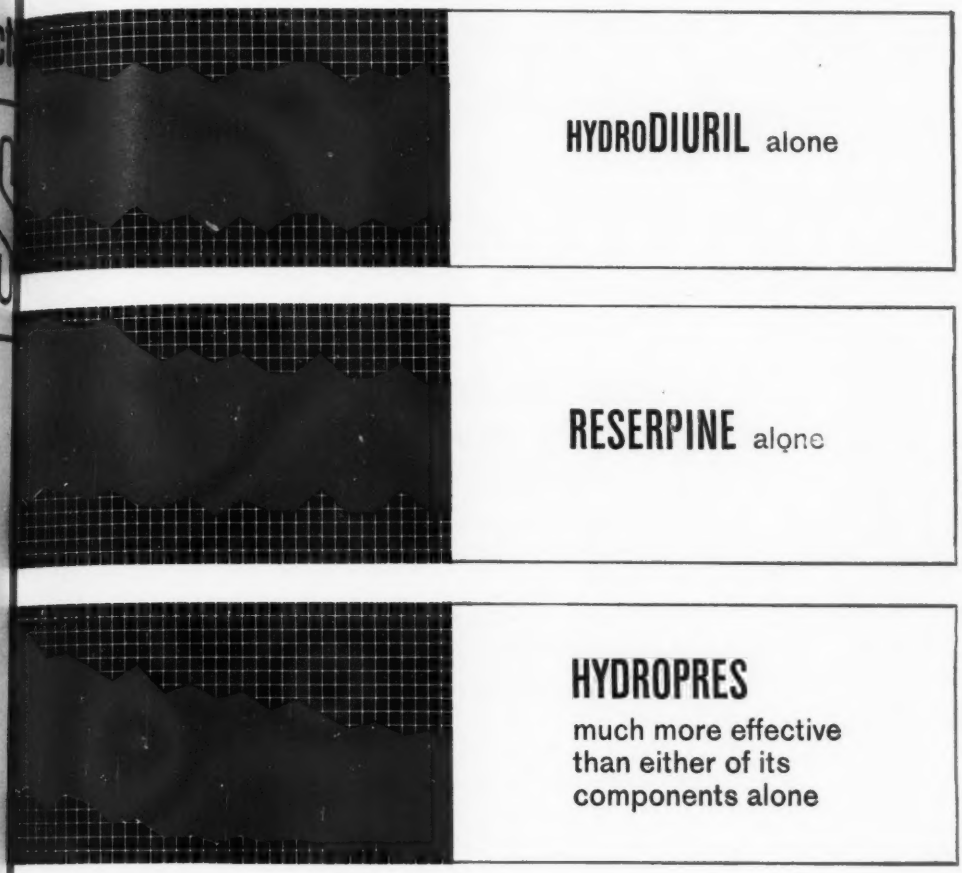
HYDRODIURIL HYDROCHLOROTHIAZIDE antihypertensive

WITH

RESERPINE antihypertensive-tranquilizer



For complete information write Professional Services, Dept. H, Merck Sharp & Dohme, West Point, Pa.



- Effective by itself in a majority of patients. Provides smooth, more trouble-free management of hypertension.
- Since HYDRODIURIL and reserpine potentiate each other, the required dosage of each is lower when given together as HYDROPRES than when either is given alone.
- HYDROPRES provides the needed and valuable tranquilizing effect of reserpine. Lower dosage may reduce such side effects of reserpine as excessive sedation and depression.
- Arrest or reversal of organic changes of hypertension may occur.
- Headache, dizziness, palpitations and tachycardia are usually promptly relieved. Anginal pain may be reduced in incidence and severity.
- With HYDROPRES, dietary salt may be liberalized.
- Convenient, controlled dosage.

HYDROPRES-25
25 mg. HYDRODIURIL, 0.125 mg. reserpine.
One tablet one to four times a day.

HYDROPRES-50
50 mg. HYDRODIURIL, 0.125 mg. reserpine.
One tablet one or two times a day.

If the patient is receiving ganglion blocking drugs or hydralazine, their dosage must be cut in half when HYDROPRES is added.

MSD **MERCK SHARP & DOHME,** DIVISION OF MERCK & CO., INC., PHILADELPHIA 1, PA.

*HYDRODIURIL AND HYDROPRES ARE TRADEMARKS OF MERCK & CO., INC.

the orally effective
uterine relaxing hormone

Lutrexin® TABLETS

(H.W.&D. brand of lututrin)

IN PREMATURE LABOR
THREATENED AND HABITUAL ABORTION
AND DYSMENORRHEA

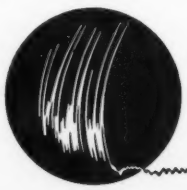
LUTREXIN has been used successfully in functional dysmenorrhea[1,2] for the past six years, as well as in selected cases of premature labor[3,4,5] and threatened and habitual abortion.[6,7]

LUTREXIN exerts an indirect, as well as a direct, relaxing action on the uterus by blocking the pituitary hormones.[8]

LUTREXIN administered orally decreases uterine contractions within thirty minutes.[1,9]

LUTREXIN is a naturally occurring, non-steroid, uterine relaxing hormone, biochemically different from other ovarian hormones.

1. *Jones, G. S. and Smith, F.: Am. J. Obstet. Gynecol., Vol. 67, No. 3, 628-633, 1954.*
2. *Jones, Scott S.: Northwest Medicine, Vol. 54, 1253-1254, 1955.*
3. *Majewski, J. T. and Jennings, T.: Obstetrics & Gynecology, Vol. 5, No. 5, 1955.*
4. *Majewski, J. T. and Jennings, T.: Obstetrics & Gynecology, Vol. 9, No. 3, 1957.*
5. *Rezek, G. H.: Annals of The N.Y. Academy of Sciences, Vol. 75, 995-997, 1959.*
6. *Hardy, E. D.: to be published.*
7. *Trythall, S.W.: The Journal-Mich. State Med. Soc., p. 711, 1958.*
8. *Bryant, H. H.: to be published.*
9. *Bryant, H. H.: Annals of The N.Y. Academy of Sciences, Vol. 75, 1037-1038, 1959.*



in vivo measurement
of LUTREXIN on
contracting uterine muscle

HYNSON, WESTCOTT & DUNNING, INC. HWD BALTIMORE 1, MARYLAND

Southern Medical Journal

PUBLISHED BY SOUTHERN MEDICAL ASSOCIATION

August 1959

The Problem of Hemorrhage Following Massive Transfusions*

ROBERT M. BIRD, M.D., and
JAMES F. HAMMARSTEN, M.D.,† *Oklahoma City, Okla.*

A disturbing matter is the massive oozing which may occasionally follow the use of great quantities of transfused blood. Defects in the clotting mechanism play a part in this complication.

UNEXPECTED AND WIDESPREAD OOZING of blood from exposed tissues may develop during major subtractive surgery. Since this complication may be seen in patients who have had no previous hemorrhagic tendency, the question has been raised as to the role of transfused whole blood as a precipitating factor.[1] The purpose of this paper is to present a few typical clinical experiences with this problem and to review briefly current thinking as to its genesis and management.

Clinical Material

During a one year period 6 patients were seen in consultation because of the development of unexpected hemorrhage during or immediately following a surgical procedure. The absence of a history of a previous hemorrhagic tendency was common to all. Each had received whole blood by transfusion before the bleeding was noted. In none was there direct evidence for blood incompatibilities. In all the amount of tissue oozing was severe.

The general problem can be illustrated by the following experience.

A 53 year old white man, an alcoholic for 25 years, was admitted with pulmonary tuberculosis for a lobectomy. He had received therapy, including several antituberculous drugs, at other hospitals. There was a history of recurrent hemoptysis and progressive weakness for only 3 months.

Bilateral apical infiltration with cavitation on the left was seen on x-ray examination of the chest. Sputum cultures were positive for acid-fast bacilli. For the 2 months prior to operation the patient was given isonicotinic acid and para-amino-salicylic acid in conventional dosages.

The following laboratory studies are pertinent to the present considerations. The vital capacity was modestly reduced, 3.7 liters, but the 1 sec. vital capacity was 65% of the total. The cephalin flocculation was negative and the bromsulphalein retention was 4 per cent. Platelets numbered 320,000 per cm., the bleeding time was 1 min., 30 sec., the clotting time, 4 min.

A left upper lobectomy was performed with no unusual complication noted; 2,000 ml. of whole blood were given during the operative procedure which lasted 3 hours. Two hours following the completion of the operation, the patient went into shock and large quantities of blood began flowing from the intrathoracic drainage tubes. An additional 3,000 ml. of whole blood were administered and the patient was re-explored. No pulsatile bleeding was noted but the entire operative site wept blood. Attempts at local hemostasis were unsuccessful and the bleeding continued. Constant transfusions were required to maintain an adequate blood pressure. In addition, the patient was given vitamin K-1, calcium gluconate, protamine and human fibrinogen, all in appropriate dosages.

Eighteen hours after the onset of the hemorrhage, the following measurements of clotting were obtained: bleeding time, 16 min.; silicone clotting time, no clot; platelets, 40,000 per cu. mm.; one stage prothrombin time, 175 sec.; impaired prothrombin utilization; fibrinogen, 528 mg.%; and calcium, 4.4 mEq./L.

The drainage tubes were clamped and thrombin was

*Chairman's Address, read before the Section on Medicine, Southern Medical Association, Fifty-Second Annual Meeting, New Orleans, La., November 3-6, 1958.

†From the Department of Medicine, University of Oklahoma Medical Center and Medical Service, Veterans Administration Hospital, Oklahoma City, Okla.

TABLE 1

BLEEDING AT SURGERY → HEMATOLOGY CONSULTATION

Diagnosis	*Operation*	*Shock During Surgery*	*Amt. of Blood Before Oozing*	*Clotting Defect*
Bronchiectasis	Lobectomy	Yes	2,000	Thrombocytopenia (Icteric serum)
Bronchiectasis	Thoracotomy	Yes	1,100	Thrombocytopenia Fibrinogenopenia (Plasma Hgb. up)
Tuberculosis (Alcoholic)*	Lobectomy	No	2,000	Thrombocytopenia Hypoprothrombinemia ? Other
Cervical Carcinoma	Radical pelvic	Yes	4,000	Thrombocytopenia Fibrinogenopenia (Icteric serum)
Pregnancy Prolapsed cord	Internal version	Yes	2,500**	Fibrinogenopenia Factor V
Cholecystitis Pancreatitis	Cholecystectomy	Yes	2,500	Fibrinogenopenia

*See text
**Postoperative

introduced into the thoracic cavity. No further whole blood was transfused but instead human albumin solution was infused. The blood pressure became stable and the patient maintained an adequate urinary output. During the next 36 hours, there was no evidence of further bleeding and vital functions were maintained satisfactorily. The hemoglobin was 6.6 Gm. and the one stage prothrombin time was normal.

The patient died suddenly and unexpectedly. No fresh bleeding was noted at necropsy and no obvious cause of death was apparent.

Comment. It was the clinical opinion that despite successful control of the bleeding, the hemoglobin had been maintained at too low a level, and that the patient had developed hypoxia with sudden death. The study of Linner[2] is certainly pertinent to this case. He showed that para-amino-salicylic acid in therapeutic dosages produced a modest prolongation of the prothrombin time in most patients. It is entirely possible that in some patients the abnormality may be of a degree to become clinically important. Perhaps the initial difficulty in our patient was precipitated by para-amino-salicylic acid. Certainly any patient receiving this drug deserves a prothrombin time determination prior to operation so corrective measures can be instituted if the time is prolonged.

Pertinent points relating to all 6 cases are presented in table 1. It is noteworthy that pulmonary or pelvic surgery was involved in 5 cases and that the sixth had a complicating pancreatitis. The amount of blood transfused before oozing was variable. Thrombocytopenia was noted in 4, intravascular hemolysis was suspected in 3, and a variety of clotting abnormalities were scattered among the several cases. Although this experience is small, it is in keeping with observations reported by others.[3-5]

To see if surgery was an essential ingredient of this problem, 50 cases were selected at random. Common to all cases was the fact that each patient had received at least 2,500 ml. of whole blood by transfusion within a single 24 hour period. An analysis of these cases is presented in table 2. Although the differences shown are not statistically significant, the data suggests two inferences. The amount of blood administered does not appear to be the critical factor in precipitating bleeding. The nature of the primary disease, especially the organ system involved, seems more important as an etiologic factor than the operative intervention.

Discussion

Stefanini[1] reported that thrombocytopenia was regularly produced by replacement transfusions. This as well as increased capillary fragility and deficiencies of accelerator factors were all considered as potentially contributing to the development of unexpected bleeding. Scott and Crosby[3] measured changes in the

TABLE 2

RANDOM SELECTION OF PATIENTS RECEIVING 2,500 ml. WHOLE BLOOD OR MORE IN 24 HOURS
TOTAL = 50 CASES

	Oozer (7 cases)	*Nonoozer (43 cases)*
Peptic ulcer	14%	46%
Operation	86%	84%
Shock	86%	86%
Blood > 5,000 ml.	43%	40%
Mortality	86%	56%

clotting mechanism observed in Korean War casualties who required unusually large quantities of stored blood. Two other groups[4,5] have recently reported their detailed studies of the bleeding defects noted in patients undergoing major surgery and receiving multiple blood transfusions.

It is the concensus that no single factor is responsible for the unexpected bleeding which may complicate the clinical picture. Most patients tolerate the administration of large quantities of whole blood without the development of a bleeding diathesis. Although a fall in platelets parallels the amount of bank blood transfused, the degree of fall is usually not alarming. Aside from the depression in the platelet counts, no single abnormality in the clotting mechanism has been common to all cases who develop bleeding. The workers at Memorial Hospital[5] noted that surgical procedures involving the liver were particularly prone to be complicated by oozing. To this organ system we would add the pulmonary and genitourinary systems. Essentially similar conclusions have been emphasized by Ulin.[6] In discussing the genesis of the oozing, the possibility of blood incompatibilities must be considered. Although no erythrocyte type specific incompatibility was seen in the 6 cases reported here, the icteric serum observed in 3 of our patients suggested excessive intravascular hemolysis. That such accidents may arise from leukocyte or platelet incompatibilities[7] is a possibility which is at present not answered.

Summary

1. Oozing may complicate conditions which necessitate massive blood replacement (i.e., greater than 2,500 ml. of whole blood).

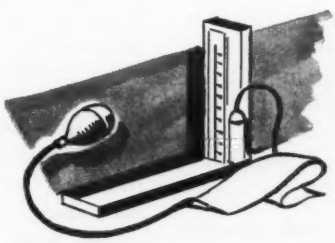
2. The basic disease or the nature of the surgical procedure are of major importance in the pathogenesis of the oozing.

3. Blood replacement itself is not the sole cause of the hemorrhagic complication. Varying defects in the clotting mechanism have been demonstrated. The most common of these are low platelets, decreased fibrinogen and accelerator factor deficiencies.

4. If oozing develops and is thought to be associated with the transfused blood, it seems advisable to limit additional blood to that which is reasonably fresh and which has been collected in nonwettable containers. Specific defects should be treated when these are recognized. Human albumin solution may be of considerable help as plasma expander if used with other appropriate measures.

References

1. Stefanini, M., Mednicoff, I. B., Salomon, L., and Campbell, E. W.: Thrombocytopenia of Replacement Transfusion: A Cause of Surgical Bleeding, (Abst.) Clin. Res. Proc. 2:61, 1954.
2. Linner, J. H.: A Study of the Effect of Para-aminosalicylic Acid on Blood Coagulation and Prothrombin Concentration on Patients with Tuberculosis, J. Thoracic Surg. 28:103, 1954.
3. Scott, R., Jr., and Crosby, W. H.: Changes in Coagulation Mechanism Following Wounding and Resuscitation with Stored Blood; Study of Battle Casualties in Korea, Blood 9:609, 1954.
4. Krevans, J. R., and Jackson, D. P.: Hemorrhagic Disorder Following Massive Whole Blood Transfusions, J.A.M.A. 159:171, 1955.
5. Zucker, M. B., Siegel, M., Cliffton, E. E., Bellville, J. W., Howland, W. S., and Grossi, C. E.: Generalized Excessive Oozing in Patients Undergoing Major Surgery and Receiving Multiple Blood Transfusion, J. Lab. & Clin. Med. 50:849, 1957.
6. Ulin, A. W., Gollub, S. W., Witchell, H. S., and Ehrlich, E. W.: Hemorrhage and Massive Transfusion, J.A.M.A. 168:1971, 1958.
7. Brittingham, T. E., and Chaplin, H., Jr.: Febrile Transfusion Reactions Caused by Sensitivity to Donor Leukocytes and Platelets, J.A.M.A. 165:819, 1957.



Diverticulum of the Female Urethra:

With Special Reference to Diverticular Carcinoma*

WILLIAM NILES WISHARD, JR., M.D., MYRON H. NOURSE, M.D., and JOHN H. O. MERTZ, M.D.,† *Indianapolis, Ind.*

Diverticulum is being recognized more frequently as the urologist searches for the lesion. Carcinoma as a complication is quite rare.

In 1805, Hey[1] reported the case of Ann Miller whom he had treated at the General Infirmary of Leeds in 1786 for an irregular purulent vaginal discharge. He found an "enlargement of the bulbous part of the urethra," pressure on which extruded pus from the external meatus. A probe passed into the meatus entered this mass and could be felt through the vaginal wall. He made a longitudinal incision in the vaginal wall, evacuated the pus, packed the cavity with lint, and closed the incision with resultant cure. This is the first record we have found of urethral diverticulum in the female.

Over 100 years later, Kelly,[2] using the words urethral diverticulum and suburethral abscess more or less synonymously, reported using the Hey operation on two patients, one with recovery and the other with the development of a urethrovaginal fistula. Kelly also discussed the subject of carcinoma of the female urethra and of periurethral carcinoma, but made no mention of carcinoma in a diverticulum. We have searched the literature since the first volume of the Index Medicus (which precedes the publication of Kelly's text by a number of years), finding the first reference to carcinoma in a diverticulum in the paper of Hamilton and Leach[3] in 1951. We[4] operated on a similar patient in 1949, thinking at the time that our paper would report the first case. Before our paper was finally published in 1952 we discovered the report of Hamilton and Leach. Their patient was operated on in 1948, thus being the first case and the first report. Since these two papers, two others have been published by Brown[5] and Roth.[6] In the meantime, we have had one more patient and have learned of another case soon to be reported by Melnick.[7] This brings the total to six, too many to be ignored. We are sure there must be more, though we have found no reference to carcinoma of the urethra and coincidental diverticulum. By 1952 there were 338 reported cases of carcinoma of the female urethra. Since then the list has increased to over 500.

Our only apology for discussing a subject of which the literature is already replete with references is that urethral diverticulum in the female must be an expanding topic; or that urologists are using their panendoscopes to more advantage. Urethral diverticulum, prior to 10 years ago, was a relatively infrequent finding in our experience. Since then we have observed 35 patients (one a male), 30 of whom form the basis of this report; 25 of these have been found in the last 4 years.

Etiology and Pathology

Etiology. Johnson[8] believes that trauma associated with intercourse and delivery are factors in causing urethral diverticula. In 1938, he found only one report of a diverticulum in a virgin, although he had one in a newborn. Half of our patients were never pregnant, one never married. Johnson lists as other possible causes: (*acquired*) infection of urethral glands with a sealing off and abscess formation followed by opening into the urethra, instrumentation and fulguration, stricture, and urethral stone; (*congenital*) Gärtner's duct, cysts formed by faulty union of primal folds, cell rests, wolffian duct and vaginal cysts. Krieger and Poutasse,[9] in 1954, reported 49 cases at the Cleveland Clinic.

*Read before the Section on Urology, Southern Medical Association, Fifty-Second Annual Meeting, New Orleans, La., November 3-6, 1958.

†From the Department of Genito-Urinary Surgery, Indiana University School of Medicine and Indiana Methodist Hospital, Indianapolis, Ind.

They believe trauma is a factor as well as infection in the paraurethral glands resulting in closure, abscess formation, and rupture into the urethra.

Many authors agree that urethral diverticulum is a frequent source of chronic infection of the lower urinary tract. The upper tract is usually normal. Cook[10] has reported well over 70 patients from the Mayo Clinic. The etiology of carcinoma in a urethral diverticulum must be the same unknown as carcinoma of the urethra.

Pathology. We believe that suburethral abscess and diverticulum are closely related, the former being a premature diverticulum which has not established urethral communication. The communication may be missed by endoscopy only to be found later at operation. Our experience has been that all but three opened in the middle or distal third of the urethra. The opening may be from 1 to 12 mm. in size. The diverticulum may be only a centimeter in diameter or extend the full length of the urethra, even undermining the trigone. They may be single or multiple, and while usually found between the anterior vaginal wall and beneath the urethra, they may be lateral or even anterior. Epithelium (usually transitional) may or may not be found lining the sac when examined by the pathologist. Fibrous walls are always present, sometimes (20% in our experience) with a muscular element also. The sac may or may not contain pus, mucus, urine, stone, blood or tumor at the time it is examined. The perceptibility of the sac depends on its fluid content. Stones may be contained in the sac (2 or 7% in our series). Carcinoma, if present (also 7% in our series), has been reported to be transitional cell (3 cases), adenocarcinoma (2 cases), and epidermoid carcinoma (1 case). Three of the 6 reported cases of carcinoma in a diverticulum have invaded the urethra. We have recently seen one patient with a carcinoma of the urethra and an uninvolved diverticulum. Although we have seen no instance of rupture of a diverticulum into the vagina, one of our 2 patients with diverticular carcinoma has had vaginal invasion.

Incidence

Urethral diverticulum seems to be an increasingly prevalent lesion in spite of its 172 year history, the literature having increased greatly in the last 20 years. Brown[5] reports an incidence of about 0.35 per cent. We suspect ours is about the same. Gilbert and Cintron[11] found that the subject is not included in the teaching of 50 medical schools. They state that the average patient sees 9.5 physicians before the diagnosis is made. In 102 bibliographic references they found only one case[8] of carcinoma in a diverticulum. Five others have been mentioned above, all since 1951. Others must have been seen but not reported. Still more have probably not been detected until late and reported as carcinoma of the urethra or vagina, the true etiology having been missed because the lesion was seen at too late a stage of the disease. Gilbert and Cintron emphasize that the urologist must be "diverticulum conscious," a point brought out previously by our late beloved T. D. Moore. Our patients ages varied from 29 to 70 years, the average being 51 years; 14 were over, and 16 under the average.

Diagnosis

Symptoms. Practically every symptom referable to the lower urinary tract may be provoked by urethral diverticula. The symptoms may be acute or chronic, constant or intermittent. They include frequency, nocturia, urethral burning, urinary difficulty, incomplete emptying of the bladder or retention, hematuria, seepage of pus from the meatus, incontinence, urgency, dyspareunia, suprapubic distress, sense of pelvic pressure, bladder spasms, malaise, fever, strangury, urethral tenderness and mass.

Coincidental unrelated lesions. Among our patients we have found additional disease as follows: bladder tumor (1), urethral carcinoma (1), pyelonephritis (3), gallstones (3), pneumaturia due to sigmoidal diverticulitis with vesicocolonic fistula (1), sigmoidal diverticulosis (1), nonrotated kidney (1), trichomonas vaginalis (1), hypertension (3), vulvar leukoplakia (1), and fistula-in-ano (1). Seventeen of our patients have had pelvic operations, 14 of which were hysterectomies (all for nonmalignant disease). This is a very high incidence, though it is hard to believe there is any casual relationship. Seven of our patients had a family history of cancer, but both those

with diverticular carcinoma had a negative family history.

Physical findings. A vaginal mass may or may not be present at the time of examination. Its presence is dependent on the presence of pus, mucus, urine, blood, stone, or tumor in the diverticulum. If the diverticulum is deflated or too small no mass will be palpable between the vagina and urethra. The mass may or may not be tender. Pus, urine, blood, or mucus may be expressed (if present) from the meatus by pressure on the mass. If diverticula carcinoma is present, in 50% of the patients tumor tissue has been expressible from the meatus by vaginal pressure. Crepitus may be felt if multiple stones are present.

Laboratory findings. The only significant laboratory findings have been pyuria, hematuria and bacteruria. Here again is a variable factor not always present. Twenty-five per cent of our patients had a normal urine. One had mild azotemia due to chronic pyelonephritis. None had elevated white blood counts. Serologic test for syphilis was positive in one. Trichomonads were found in one. Biopsy of colloid urethral discharge in one showed transitional cell carcinoma.

X-ray findings. The upper urinary tract has been significantly normal in most of our patients, and the cystogram likewise. Urethrography has demonstrated the diverticulum in 75% of the cases where it has been employed (12 patients). We have tried various occluding catheters and find that a blunt nosed Asepto syringe loaded with one ounce of 90% Miokon is the simplest and gives the best results. The syringe is placed against the meatus, exposure being made shortly after injection is started while the solution is still flowing into the urethra. Cook[10] has used a coiled ureteral catheter inserted in the diverticulum to advantage, but we have found it difficult to keep in place. In one instance where we were unable to visualize the urethral connection with a panendoscope, we injected the sac with indigo carmine through the vagina. This helped not at all. We see no reason, however, why a .25 guage needle could not be introduced from the vaginal side under observation and the diverticulum be injected with radio-opaque media to good advantage. We have not actually tried this but expect to in the future. X-ray study has detected stone in one diverticulum and failed in another. Voiding urethrograms may be of help.[12]

Endoscopic findings. Exclusive use of a cystoscope will result in failure of detection of most diverticula. Kelly[2] was finding them 64 years ago with a plain endoscope and reflected light from a head mirror. The panendoscope is the preferred instrument. A 28 F. sheath is preferable, smaller ones being less likely to separate the urethral walls sufficiently to visualize the opening. The physician should be "diverticulum minded" in the first place because all stomas are not large enough to be visualized readily nor do they bear a sign post. For a definitive examination, particularly if a tender mass is palpable in the urethrovaginal septum, anesthesia is desirable. The opening may be only a millimeter in diameter or be over a centimeter in size. It may be only visible as a crater from which pus erupts when digital counterpressure is applied from the vaginal side. The lesion may be single (92%) or multiple (8%). It may be on the floor of the urethra but not necessarily so; it may be located in any portion of the urethra although we have found it in the middle or distal third in 92% of our patients. A diverticulum containing endoscopically visible stones was observed in 7% (2) of our patients and tumor in 7% (2). Independent primary carcinoma of the urethra was seen in one without diverticular invasion. Urethral stenosis was present in 12.5 per cent; and interstitial cystitis was found in one in our series. Granuloma of the urethra was seen in another. Twenty-one per cent (6) had inflammatory polypoid bodies around the vesical orifice. In 7% (2) we failed to find the opening endoscopically.

Treatment

A few diverticula are too small to require treatment but should be watched for further development. One of our patients was not operated on because of incurable carcinoma of the urethra. Another did not return, while one has been deferred for observation. One has had too few symptoms. Another was not treated surgically because of vulvar leukoplakia. The remaining 23 required operation. Conservative treatment by digital emptying of the diverticulum is only a temporizing measure. Semiconservative surgical measures (fulgurating the diverticulum or increasing the

size of its opening by endoscopic electrosurgery) are in about the same category.

Various operations have been described. The first is that of Hey,[1] already mentioned. The customary method is that of making a longitudinal incision on the anterior vaginal wall, dissecting out the diverticulum, excision, and closure of the urethral and vaginal defects in layers. A catheter should be left in for 8 to 10 days thereafter. Carson and Wells[13] suggest the use of temporary cystostomy to prevent urethrovaginal fistulas. We have done this at a third operation to remove recurrent or missed diverticula. This is the only patient we have had requiring multiple operations for removal. We have utilized excision alone 14 times. In one patient we used the Ellick[14] ablation technic, packing the diverticulum with Oxycel, and in 6 we have partially excised the diverticulum, packed with Oxycel and closed in a separate layer of sutures. Other methods have been that of Gilbert and Cintron,[11] going in suprapubically to remove diverticula on the anterior urethral surface, and that of Edwards and Beebe[15] for diverticula of the anterior half of the urethra. They report five operations without subsequent urethrovaginal fistula. Their method is to expose the diverticulum and urethra vaginally following which they incise the floor of the urethra from the meatus down to the diverticulum. The sac is excised and the urethra and vaginal wall repaired in separate layers. They claim better exposure and avoidance of fistulas by this procedure.

When carcinoma is present in a diverticulum, conservative excision of the diverticulum may suffice (as it did in our patient). Brown[5] found this satisfactory, as did Hamilton and Leach,[3] though the latter also used irradiation for urethral recurrence. Because of urethral involvement, Roth[6] had to make a permanent cystostomy, excise the entire urethra and part of the vagina. Melnick[7] used radium needles with recovery from the carcinoma, but did not remove the diverticulum. Our patients developed urethrovaginal fistulas as did Brown's patient. Roth's patient, of course, had no urethra left. Melnick did not remove the diverticulum. Hamilton and Leach thus have the only operative case without postoperative fistula.

Surgical removal of a urethral diverticulum should ordinarily be a safe procedure, though Brown[5] reports one death (due to shock) among 16 operations. Permanent postoperative incontinence has not been a factor, even with the patients developing urethrovaginal fistulas. (Thomas[2] reported a patient in 1877 with carcinoma of the urethra on whom he did a total removal of the urethra down to the vesical neck with good subsequent control of urine!)

Postoperative urethrovaginal fistulas developed in 6 of our 23 surgical patients. Two of these had diverticular carcinoma. It may be that suprapubic diversion of the urine would avoid this.[13] Krieger and Poutasse[9] report two postoperative fistulas in 35 operations. Brown[5] reported two in 16 operations. Higgins and Roen[16] report two, McCorriston[17] one. On the other hand, Kittredge[5] had none in 46 operations, Knight and Hill[18] none in 10 operations, Johnson[8] none, Gilbert and Cintron[11] none, and Cook[10] none. We have not found that this complication is disturbing nor productive of symptoms.

Results. All authors agree that complete removal of the diverticulum relieves the patients' symptoms and stops pyuria. This has been our experience, though once we had to operate three times to remove all the tissue. Hospitalization has been from 12 to 30 days. Five of the patients with diverticular carcinoma appear to have been cured. One of ours is in her ninth year and is well. Our other patient has had a pelvic recurrence, recently requiring a cordotomy for relief of pain.

Diverticular carcinoma. One of our patients has already been reported.[4] The other, a married woman of 43, was seen in consultation because of extensive urethral, vaginal and pelvic extension. She had had excision of a diverticulum containing tumor by Dr. Wm. Sigmond of Columbus, Indiana. The pathologic report was epidermoid carcinoma. She developed a recurrence which later required permanent cystostomy because of urethral obstruction. Only recently has she had to have a cordotomy for relief of pain. Irradiation has been used without avail.

Melnick's patient, a nullipara aged 50, had a mass on the anterior vaginal wall. Biopsy of tissue extruded from the diverticulum was secured endoscopically and reported as transitional cell carcinoma. He and Birdsall used

24, 1 mg. radium needles in and around the tumor, placed by vaginal approach, giving a total of 8,000 r. The diverticulum remains but the tumor is gone at the end of one year.

Brown's[5] patient was 40, and had had symptoms for 6 years. He found tumor in the diverticulum which projected in papillary fashion but proved to be adenocarcinoma. He removed the diverticulum with cure, but a urethrovaginal fistula resulted as it did in our cases.

Hamilton and Leach[3] call attention to the fact that carcinoma of the female urethra is usually transitional or squamous cell. They found a diverticular carcinoma in a 53 year old woman who had had vaginal bleeding for a year. She had a cystic mass in the anterior vaginal wall; the tumor was very soft. They think the carcinoma arose from periurethral mucous glands or misplaced nephrogenic tissue, and that the diverticulum was congenital because smooth muscle was found in its walls. Recurrences after the original operation for removal of the diverticulum and tumor required subsequent excision; irradiation was also used. The patient apparently recovered although inadequate time has elapsed to be sure of a permanent cure.

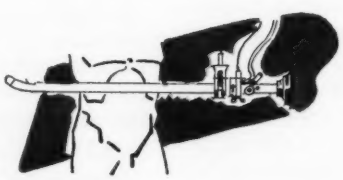
Roth's[6] patient was a 40 year old colored woman who had bleeding from the meatus during and without urination. A soft mass was palpable on the anterior vaginal wall, compression of which extruded a tumor from the meatus. It proved to be transitional cell carcinoma. Endoscopy showed tumor tissue in a diverticulum but the urethra was also involved as was the vesical neck. He removed the urethra, part of the vesical neck and vagina and did a permanent cystostomy. The patient was well 20 months later.

Summary

We have reviewed our experience with 30 urethral diverticula in the last 10 years; 25 of these have occurred in the last 4 years. Diagnosis and treatment has been discussed. Urethrovaginal fistulas have resulted too often but are not productive of serious symptoms. We have reported one new case of diverticular carcinoma and outlined the reports of the other 5 on record.

References

1. Hey, William: Practical Observations in Surgery. Philadelphia, 1805, p. 305.
2. Kelly, H. A.: Suburethral Abscess, Operative Gynecology. New York, D. Appleton & Co. Vol. 1:303, 1898.
3. Hamilton, J. D., and Leach, W. B.: Adenocarcinoma Arising in a Diverticulum of the Female Urethra, Arch. Path. 51:90, 1951.
4. Wishard, W. N., Jr., and Nourse, M. H.: Carcinoma in Diverticulum of Female Urethra, J. Urol. 68:320, 1952.
5. Brown, E. W.: Diverticulum of the Female Urethra: Report of 23 Cases with Adenocarcinoma in One, South. M. J. 49:982, 1956.
6. Roth, A. A.: Carcinoma of the Female Urethra, Ohio M. J. 51:872, 1955.
7. Melnick, J. L.: Personal Communication, Philadelphia, 1958.
8. Johnson, C. M.: Diverticula and Cyst of the Female Urethra, J. Urol. 39:506, 1938.
9. Krieger, J. S., and Poutasse, E. F.: Diverticulum of the Female Urethra, Am. J. Obst. & Gynec. 68:706, 1954.
10. Cook, E. N.: Diverticulum of the Female Urethra: Problems in Diagnosis and Treatment, Surg. Gynec. & Obst. 99:273, 1954.
11. Gilbert, C. R. A., and Cintron, F. J. R.: Urethral Diverticulum in the Female, Review of the Subject and Introduction of a Different Surgical Approach, Am. J. Obst. & Gynec. 67:616, 1954.
12. Granberg, P. O., and Svartholm, F.: Urethral Diverticulum in the Female Diagnosed by Urethrocystography, Acta chir. scandinav. 115:78, 1958.
13. Carson, R. B., and Wells, W. D.: Treatment of Female Urethral Diverticula, South. M. J. 44:285, 1951.
14. Ellick, Milo: Diverticulum of the Female Urethra: A New Method of Ablation, J. Urol. 77:243, 1957.
15. Edwards, E. A., and Beebe, R. A.: Diverticulum of Female Urethra; Review; New Procedure for Treatment; 5 Cases, Obst. & Gynec. 5:729, 1955.
16. Higgins, C. C., and Roen, P. R.: Calculus Containing Urethral Diverticulum in a Woman: Report of a Case, J. Urol. 49:715, 1943.
17. McCorriston, C. C.: Urethral Diverticulum in the Female, Postgrad. Med. 16:539, 1954.
18. Knight, J. R., and Hill, N. N., Jr.: Diverticulum of the Female Urethra, Am. J. Obst. & Gynec. 70:1214, 1955.



Diagnosis and Treatment of Injuries to the Lumbar Intervertebral Disk of Industrial Workers*

HOMER D. KIRGIS, M.D., and
RAEBURN C. LLEWELLYN, M.D.,† *New Orleans, La.*

This paper contains an excellent portrayal of the lumbar disk syndrome, its history, course and the abnormalities in the physical examination.

PERSISTENT COMPLAINT OF BACKACHE after a straining or compression injury to the lower portion of the back is common. In most of these patients there is no objective evidence of injury other than spasm of the lower paraspinous muscles. This type or degree of injury to the lower part of the back frequently causes controversy with regard to diagnosis and therapy. Specifically, the usual problem is: does the syndrome represent only a sprain or strain of the lumbar paraspinous muscles and ligaments, or is it due to injury of a lower lumbar intervertebral disk or a combination of such injuries. It is well known that the radicular or sciatic pain of the fully developed lumbar disk syndrome is preceded characteristically by a period during which the patient has only discomfort of the lower part of the back. For example, according to Bradford and Spurling,[1] "Back pain usually follows the injury much more directly than does sciatic pain, which may be quite mild or absent for several days or weeks following the injury."

The syndrome produced by a herniated lumbar intervertebral disk should therefore be considered as consisting of a primary phase during which the pain is confined to the lower portion of the back and a secondary phase when the patient experiences radicular or sciatic pain in addition to the pain in the lower part of the back. For this reason it is important to consider the probability of a pathologic alteration of the disk in patients with persistent discomfort in the lower part of the back, and to prescribe therapeutic measures that would be more appropriate than those employed in the treatment of a postulated strain or sprain of the paraspinous muscles and ligaments of the lower part of the back.

We wish to review the pertinent points usually uncovered by the neurosurgeon in interviewing and examining patients who have sustained a straining or compression injury to the lower part of the back without damage to the vertebrae and to recommend a plan of therapy for each phase of the resulting syndrome. It should be pointed out that the neurosurgeon ordinarily does not see such patients until the second phase of the syndrome.

Diagnosis

Most patients will say that the onset was at least moderately painful. The discomfort is often described as feeling as if a knife had been thrust into the back. Some describe the initial discomfort as a slightly painful slipping, tearing or burning sensation of the lower part of the back. Occasionally, the patient and even a fellow worker will have heard a popping or cracking sound of the lower part of the back. The patient may have been forced to stop working at once or he may have obtained some relief after resting for a short time and then returned to work. Many of the latter group will report that when they "cooled off" at the end of their working period, the pain recurred and was more severe than immediately after the injury.

Further questioning generally reveals the

*Read before the Section on Neurology and Psychiatry, Southern Medical Association, Fifty-second Annual Meeting, New Orleans, La., November 3-6, 1958.

†From the Department of Surgery, Division of Neurosurgery, Tulane University School of Medicine and the Section on Neurosurgery, Ochsner Clinic, New Orleans, La.

information that shortly after the injury the patient was seen by the "company doctor," who gave him some "pain medicine" and advised him to return to the office three to six times a week for applications of heat to the back. Many patients are told to sleep on the floor or a hard bed. A few, at this stage of the syndrome, will have been hospitalized for a period of complete or relatively complete bedrest and may even have received a trial of leg or pelvic traction. Many of those treated as outpatients will have had an exacerbation of the discomfort while riding a car or bus to the office. Most will report having obtained partial relief by applications of heat but again, many will have had an exacerbation of the discomfort by the trip home. The patient usually has had such treatment for several weeks before he is seen by the neurosurgeon.

These patients usually will report that several days or weeks after the injury, the pain in the back extended into the right or left gluteal area. Characteristically, it will have gradually extended into the posterior, posterolateral or lateral aspect of the thigh to the knee, then into the posterior, lateral or anterolateral aspect of the leg to the ankle and into the feet and toes. Often the patient will state that the pain extended into the "outside" (lateral three) or the "inside" (medial two) toes. Numbness and tingling may be continuous or intermittent throughout the area of pain in the extremity or possibly only in the more distal areas, as along the lateral or anterolateral aspect of the leg or of the foot and toes. Some patients report that the pain extends only to the ankle but add, "The numbness and tingling extend into the toes."

At this stage of the syndrome, most patients believe the involved extremity is weak and many will cite as an example of this, "The knee seems to give way at times." This sensation causes some patients to carry a cane. Many state they use it also "to keep some of the weight off" the painful extremity. The same reaction frequently is demonstrated in walking by the patient limping on the painful extremity and in standing by his keeping the painful extremity slightly flexed.

These patients usually prefer to sit in a firm "straight-backed chair with arms." Often the patient likes to "brace" his back against the back of the chair and to support some of the weight of the body by resting the elbows on the arms of the chair. Many report that they must change their position frequently while sitting or even get up and walk about for a brief period. Some tolerate driving or riding in a car better if they stop at intervals, get out of the car and walk about. Most patients who are experiencing severe pain in a lower extremity prefer to sit with most of the weight of the trunk on the nonpainful buttock and to keep the painful extremity partially extended while sitting in that position. Standing, walking, sitting, riding, stooping, lifting, coughing, sneezing, bowel movements and almost any type of activity requiring a significant degree of physical exertion increases the discomfort of most patients. Patients obtain the greatest degree of relief by "lying flat on their back on the floor or a hard bed." Additional relief may be obtained by placing an electric heating pad under the back and a pillow under the knee of the painful extremity while lying in this position. Lying in the horizontal decubitus position on the nonpainful side generally gives some relief but lying on the side of the painful extremity usually increases the pain. Application of liniment to the painful area of the back results in relief for many patients. Often, when these patients attempt to sleep on a firm bed, they are awakened during the night by the pain, whereupon they spend the remainder of the night sleeping on the floor. Many obtain considerable temporary relief, by "getting into a tub of hot water." Application of adhesive tape to the back or wearing a back support usually provides some relief. However, many patients will point out that the improvement continues only as long as their movements are restricted, their discomfort becoming as severe as before with removal of the support. Similarly, traction usually gives some degree of relief at least while being applied.

The greatest source of discomfort of most patients is the pain in the back even after the pain has extended throughout the length of one lower extremity. However, there may be brief periods of greater discomfort in the extremity, as after coughing or sneezing, when the pain from the back often is said to "extend like an electric shock down the leg." The pain in the back may lessen with extension of pain into the lower extremity and it even may become less severe than the pain in the extremity. Rarely, the pain in the back

may almost, if not completely, disappear after involvement of the extremity.

Patients with a history consistent with the diagnosis of lumbar disk syndrome often have sustained previous injury to the lower part of the back. The patient may have had a similar, but usually less mild, episode several months or years earlier. He may have become completely asymptomatic and remained so in spite of performing work requiring much exertion. Often, however, they report that "the back never was quite as strong as before" and add that they had continued to have mild soreness of the lower part of the back when lifting heavy objects or stooping and bending.

Although a thorough interview of the patient who has sustained an injury to the lower part of the back may reveal diagnostic information that seems conclusive, the problem can be satisfactorily evaluated only when the history is correlated with the results of a detailed physical examination and supplementary studies, such as roentgenography and possibly myelography and diskography.

An adequate clinical examination of this group of patients should include evaluation of the following:

(1) Gait
(2) Appearance
  (a) Degree of discomfort
  (b) Apparent honesty
(3) Exact position while sitting
(4) Stance
(5) Alignment of spine
  (a) Loss of lumbar lordosis
  (b) Accentuation of lumbar lordosis
  (c) Scoliosis
    (1) Convex to painful side
    (2) Concave to painful side
    (3) Varies
  (d) Kyphosis
(6) Degree of spasm of paraspinous muscles
  (a) None
  (b) Slight
  (c) Moderate
  (d) Severe
  (e) Spasm bilaterally equal or unequal
(7) Range of motility of lower spine
  (a) Normal
  (b) Slightly reduced
  (c) Moderately reduced
  (d) Greatly reduced
(8) Degree of localization of pain to pressure and percussion over the spine and paraspinous areas
(9) Radiation of pain produced by pressure and percussion over the spine and paraspinous areas
(10) Acuity of exteroception in lower extremities
  (a) In area of greatest pain
    (1) Normal
    (2) Slightly reduced
    (3) Moderately reduced
    (4) Greatly reduced
  (b) In adjacent dermatomes
    (1) Normal
    (2) Slightly reduced
    (3) Moderately reduced
    (4) Greatly reduced
(11) Acuity of proprioception
(12) Acuity of vibratory sense
  (a) Lateral malleolus
  (b) Medial malleolus
  (c) Tibial tubercle
(13) Musculotendon reflexes
  (a) Normal
  (b) Reduced
  (c) Absent
(14) Atrophy of muscles
  (a) Circumference of thigh 40 cm. proximal to tibial tubercle with lower extremities partially flexed
  (b) Circumference of leg 10 cm. distal to tibial tubercle with lower extremities partially flexed
  (c) Status of intrinsic muscles of feet
(15) Strength
  (a) Back
    Ability to perform lifting in standing, stooping or squatting position
  (b) Lower extremities
    Movements of thigh, leg, feet and toes
(16) Coordination
(17) Straight leg bending test
  Negative or slightly, moderately or severely positive for production of or exacerbation of pain in back, extremities or both areas. Angle with horizontal at which the pain is produced or exacerbated
(18) Straight leg bending plus dorsiflexion of feet
(19) Flexed leg bending test
(20) Flexion of lower extremity followed by extension of leg
(21) Popliteal pressure with the lower extremities partially flexed
(22) Extension of the leg while patient is sitting
(23) Reactions to sudden elevations of the intraspinal pressure
  (a) Deep inhalation
  (b) Valsalva's maneuver
  (c) Jugular compression
(24) Degree of cooperation by patient with interview and examination
(25) Apparent effort to exaggerate discomfort and disability

Supplementary examination should include roentgenography of the lumbar and sacral spine. Additional studies that may be indicated include lumbar spinal puncture with jugular compression, cerebrospinal fluid sur-

vey, myelography, diskography and electromyography. Usually none of the latter group of tests is indicated. Myelography and diskography should not be performed until surgical treatment is considered necessary.

Treatment

The treatment of choice in the primary stage of an injured lower back syndrome in which the most likely diagnosis is strain or sprain of the lower paraspinous muscles and ligaments or bulging of a lumbar intervertebral disk is complete or relatively complete rest on a hard bed, frequent applications of heat to the painful area of the back, administration of antispasmodics regularly and use of analgesics as needed. Gentle massage and application of liniment over the spastic paraspinous muscles may further reduce the discomfort.

If such measures do not cause significant improvement within a few weeks, injury to an intervertebral disk should be more strongly suspected and bilateral leg traction should be tried in conjunction with the treatment in progress. Traction is definitely indicated if the pain begins to descend into a lower extremity from the lower part of the back. If satisfactory relief is obtained, it seems logical that such patients be fitted with a back support upon being mobilized.

If, upon mobilization, the patient has a significant degree of pain in the lower extremity and back, he should return to bedrest and a decision should be reached regarding the advisability of another trial of the measures already used or surgical intervention.

At operation, the involved nerve should be well decompressed posteriorly by removal of a portion of the adjacent laminas and the ligamentum flavum as well as anteriorly by removal of the herniated portion of the disk. Curettement of the vertebral surfaces adjacent to the pathologic intervertebral disk should be performed and additional fragments of disk tissue removed. This, of course, reduces the chances of recurrence of the nerve root compression by later extrusion of a fragment of the residual disk tissue.

Postoperative convalescence will be hastened by application of heat to the lower part of the back beginning on the first postoperative day. Usually the patient is allowed to be out of bed on the third or fourth postoperative day and exercises are begun under the supervision of the physical therapist. Applications of heat and exercises are continued until the patient is discharged from the hospital approximately one week after operation; the patient is advised to continue these measures at home for 2 to 4 weeks, depending on the duration of the residual soreness in the back. He usually is allowed to resume light work from 4 to 8 weeks after discharge from the hospital and is advised not to perform work requiring heavy lifting until 4 to 6 months later.

Summary

The importance of a detailed history and physical examination of the industrial worker who complains of pain in the lower part of the back has been emphasized. Correlation of the results of these portions of the investigation with roentgenograms of the lumbar and sacral spine usually establishes the diagnosis. Infrequently, myelography, diskography or additional diagnostic tests are necessary.

The syndrome produced by a herniated lumbar intervertebral disk characteristically consists of a primary phase in which the discomfort is confined to the lower part of the back and a secondary phase in which the patient experiences radicular pain in one lower extremity in addition to the pain in the lower part of the back. Such patients cannot be adequately treated completely on an outpatient basis.

Reference

1. Bradford, F. K., and Spurling, R. G.: The Intervertebral Disk. Springfield, Ill., Charles C. Thomas, Publisher, 1947.

Discussion (Abstract)

Dr. Edward A. Attix, Hattiesburg, Miss. It gives me great pleasure to have the opportunity to discuss this excellent paper which Drs. Kirgis and Llewellyn have presented. Being the only orthopedic surgeon to speak at this Section I suspect I am supposed to serve as some sort of abrasive.

Naturally, as an orthopedic surgeon, I have some considerably different ideas about the causes and treatment of painful conditions in the spine. One of the things which appears to impress orthopedic surgeons more than neurosurgeons perhaps, is the fact that there are so many conditions which may mimic the ruptured disk syndrome. Notable among these is what we have chosen to call the lumbosacral facet syndrome. In this condition, which is related to degeneration of the lumbar disk, the patient experiences momentary episodes of "locking" of the facet joints. When this occurs the patient is unable to stand erect and has

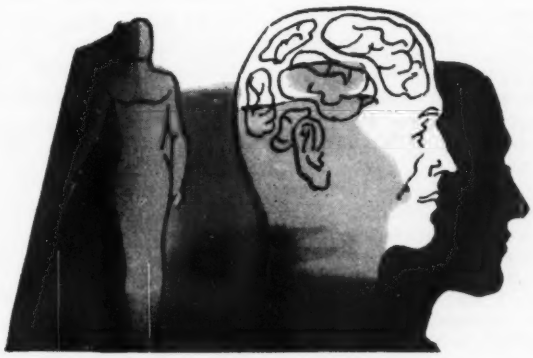
severe pain which he usually localizes in the lumbosacral area. I believe that these are the patients who have benefited by chiropractic or osteopathic manipulation. The term lumbosacral facet syndrome is used because of the fact that, since the lumbosacral disk degenerates more rapidly than any other in most cases, the "locking" episodes usually occur at the level of the lumbosacral facets.

In addition, there are several other conditions such as lumbosacral instability and spondylolisthesis which may cause pain in the lumbosacral area. Dr. Kirgis did not appear to be concerned about differentiating between what has been called "referred" pain and true radiating or radicular pain in the lower extremities. Kellgren, in the late 1930's, pointed out the fact that the origin of the *deep* pain sensation in the central nervous system is according to sclerotomes or somatomes rather than on the basis of dermatomes. These somatomes have no relation to the pattern of the dermatomes. A patient with a painful condition in some deep structure in the back may experience "referred" pain in the lower extremity in the distribution of the particular somatome involved. On the basis of the patient's history, it is impossible to differentiate "referred" pain from true radicular pain due to nerve root compression. In this regard I must mention that this paper appeared to suggest that the patients might be expected to feel pain in the region of the particular dermatome involved in the nerve root compression. I do not believe this is so and feel there is sufficient scientific evidence to indicate the contrary. However, I may have misinterpreted Dr. Kirgis' meaning.

I was delighted to note the authors employ the posterior tibial nerve test which was devised by Cram and which I believe is extremely valuable. It does not appear to have gained very widespread recognition but it certainly merits it.

There is one final consideration I wish to bring out and will pose as a question to Dr. Kirgis. Am I correct in assuming from your statements that you quite frequently operate in industrial injuries with a clinical diagnosis of a herniated disk without having had a positive myelogram indicating such a defect?

Dr. Llewellyn (Closing). We never perform myelography on patients whose history and clinical and roentgenographic findings are characteristic of injury of the lower lumbar disk. In atypical cases myelography is done, and we rarely, if ever, operate if the results are negative.



CASE REPORT

Human Leptospiral Infection Due to One of the *Leptospira Australis A* Group: Report of a Case in the United States*

JOHN AMMONS, M.D., MILDRED M. GALTON, Sc.M.,
L. E. STARR, D.V.M., Ph.D., R. W. MENGES, D.V.M.,
and CHARLES LeMAISTRE, M.D.,† *Atlanta, Ga.*

HUMAN INFECTION with *Leptospira australis A,* Ballico, has not been detected previously in the United States, although this serotype has recently been isolated in Georgia from both racoons and an opossum.[1] A white schoolboy with clinical and serologic evidence of *Lept. australis A,* Ballico, infection has been studied and epidemiologic investigation conducted. These form the basis of the present report.

Case Report

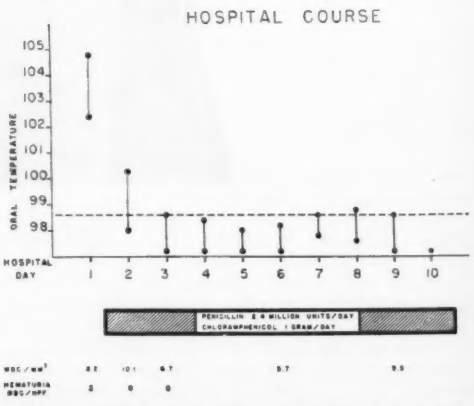
A 14 year old schoolboy swam in a creek 10 days prior to hospitalization. One day before admission he awoke with malaise. Several hours later generalized headache and bilateral pain developed in the calves, knees, and thighs. The pain in the lower extremities was markedly aggravated by movement. Nausea and vomiting, followed by chills and fever, were first noted in the evening of the day of onset. The following day, after 36 hours of clinical illness, the boy was admitted to Grady Memorial Hospital.

On admission, the rectal temperature was 104°F. He appeared acutely ill and moderately lethargic. A generalized rash was present, most marked over the trunk, extremities, and face. There was no eruption on the palms or soles. Each circumscribed maculopapular eruption measured 0.5 to 1 cm. in diameter and blanched on pressure. The pharynx was diffusely injected without exudate. Conjunctivitis, jaundice, joint tenderness or swelling were not detected. EKG on admission was within normal limits. The initial total leukocyte count was 8,200 per cu. mm. with a normal differential picture. The sedimentation rate was 41 mm. per hour. Initial urinalysis revealed 3 RBC per hpf., but no albumin was detected. Cerebrospinal fluid findings were within normal limits with the exception of a leukocyte count which revealed 12 lymphocytes per hpf.

Fever characterized the first two days after admission, ranging as high as 105°F. on the first day. The patient was begun on procaine penicillin, 600,000 units every 4 hours and chloramphenicol, 250 mg. every 6 hours. On the second day of hospitalization, the highest recorded temperature was 100°F., and thereafter the temperature was within normal limits. It is noteworthy that marked subjective improvement occurred on the morning of the second hospital day. The clinical course is depicted in figure 1. It is worthy of note that a mild secondary rise in temperature occurred between the 7th and 9th days of hospitalization.

Skin biopsy of the rash showed a mild perivascular, acute inflammation. Muscle biopsy, however, was unremarkable. Hepatic function tests were within normal limits and serologic tests for bacterial infec-

FIG. 1

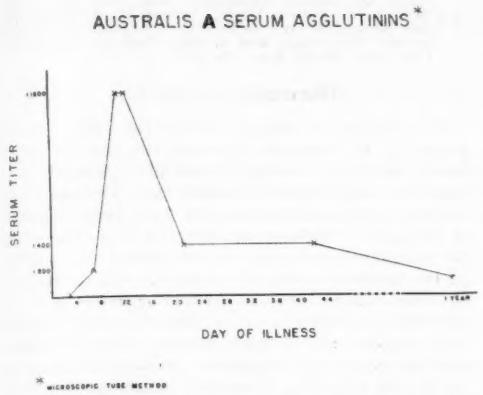


Clinical course in hospital. Note suggestion of secondary temperature elevation between the 7th and 9th day.

*Read before the Section on Public Health, Southern Medical Association, Fifty-Second Annual Meeting, New Orleans, La., November 3-6, 1958.

†From the Departments of Medicine, Preventive Medicine and Community Health, Emory University School of Medicine, and the Grady Memorial Hospital; the Georgia Department of Public Health, and the Leptospirosis Laboratory, Communicable Disease Center, (DHEW) U.S.P.H.S., Atlanta, Ga.

FIG. 2



Serologic evidence of *Leptospira australis A*, Ballico, infection as obtained by the microscopic tube agglutination with live antigen.

tion were negative. The patient was discharged on the 10th hospital day and has remained well.

Serum obtained on the 3rd day after onset was negative when tested with leptospiral antigens by the macroscopic slide agglutination technic.[2] Serum collected on the 7th day of illness, however, showed a positive slide test with *Lept. australis A* antigen and, when tested by microscopic agglutination technic with live antigen, showed a titer of 1:200. In figure 2 is shown the serologic evidence of *Lept. australis A*, Ballico, infection as determined by the microscopic tube agglutination technic. The initial titer of 1:200 on the 3rd day increased to 1:1600 by the 10th day. The titer fell from 1:1600 on the 12th day to 1:400 2 weeks later, at which level the titer remained. One year later, the titer was found to be 1:128. There was no significant reaction with antigens of seventeen other leptospiral serotypes. Leptospires were not isolated from a blood culture or urine culture.

Discussion

The patient herein reported represents the first recorded evidence of *Lept. australis A* infection in man in North America. This infection has long been recognized in Australia, however, and a brief review of the available clinical information seems in order.

Characteristic clinical findings which might identify *Lept. australis A* infection from those caused by other leptospiral serotypes have not been detected. Onset is usually sudden and is marked by headache, fever, and prostration. Doherty[3] has recently summarized the signs and symptoms seen in 38 human infections due to *Lept. australis A*. Headache, muscle pain, and chills were the most common symptoms. Abdominal pain and vomiting were also frequent. The order of frequency for the occurrence of signs of *Lept. australis A* infection is shown in table 1. Right upper quadrant tenderness, conjunctivitis, and albuminuria were the most frequent signs. It is of particular interest that skin rash and hematuria were not commonly seen.

Fever is universal and oral temperatures early in the illness are nearly always above 103°F. The duration of the febrile state varies from 4 to 8 days, tending to be of shorter duration in those patients treated with penicillin. It is noteworthy that a secondary rise in temperature as noted in our case was also seen in about one half of Doherty's cases (Fig. 1). The mild secondary rise occurred between the fifth and fifteenth day, and was not accompanied by recrudescence of symptoms.

Infections from leptospiral serotypes usually occur in an epidemic setting. In Australia, the infections caused by *Lept. australis A* and *B* have been termed "Canefield fever." Contamination of water in the canefields by the urine of rats with subsequent entrance through abrasions in the human skin is the mode of most frequent transmission. Several other animal reservoirs of infection have been detected, but the incidence of human infection derived from these sources has not yet been adequately determined. Among the known hosts are dogs, racoons, and opossums.

Epidemiologic investigation located the creek in which the patient swam, the locale being only a few miles from the Atlanta suburbs.[4] The creek ran through a pasture near a thickly wooded area. Fox and racoon tracks were found on the bank of the creek. This finding is especially pertinent because the initial identification of *Lept. australis A* was by Galton and her associates from racoons in South Georgia.[1]

From several species of wild and domesticated animals in this area, blood and sera

TABLE 1

FREQUENCY OF SIGNS IN 38 PATIENTS INFECTED WITH *LEPTOSPIRA AUSTRALIS A* AS REPORTED BY DOHERTY[3]

Sign	*Number Cases*
Right upper quadrant tenderness	13
Conjunctivitis	10
Albuminuria	9
Nuchal rigidity	3
Macular rash	2
Epistaxis	1
Hematuria	1

were obtained for culture and serologic testing. Unfortunately, neither serologic nor cultural evidence of *Lept. australis A* infection was obtained from any animal. However, another serotype, *Leptospira ballum,* was isolated from an opossum. It does seem likely, however, that the patient herein reported became infected while swimming in water previously contaminated by animals.

Summary

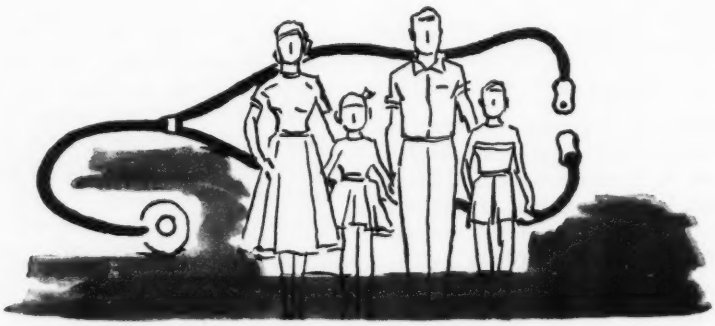
In summary, a patient with leptospirosis due to a member of the *Lept. australis A* serogroup has been reported. This is believed to represent the first detected human infection with a member of this serogroup in North America.

References

1. Galton, M. M., Powers, D. K., McKeever, S., and Gorman, G. W.: The Identification of Two Leptospiral Serotypes New To The United States, Pub. Health Rep. 72:431, 1957.
2. Galton, M. M., Powers, D. K., Hall, A. D., and Cornell, R. G.: A Rapid Macroscopic Slide Screening Test for the Serodiagnosis of Leptospirosis, Am. J. Vet. Res. 19:505, 1958.
3. Doherty, R. L.: A Clinical Study of Leptospirosis in North Queensland, Australasian Ann. Med. 4:53, 1955.
4. Starr, L. E., Galton, M. M., Ammons, J., LeMaistre, C., and Menges, R. W.: *Leptospirosis Australis A* Infection in the United States With Serologic Evidence of a Human Case, Pub. Health Rep. (In print).

Discussion (Abstract)

Mrs. Mildred M. Galton, Atlanta, Ga. This case reported by Dr. Ammons illustrates the need for diagnostic laboratories to employ multiple leptospiral antigens in serologic tests for leptospirosis. Certainly, laboratory confirmation would not have been obtained in this patient without the inclusion of a member of the australis A serogroup in our battery of antigens. As Dr. Ammons mentioned, *Lept. australis A* (Ballico) has been isolated from racoons and opossums in Georgia. More recently, we have recovered this serotype from racoons and a grey fox in North Carolina. Serologic evidence has suggested infection with a member of this serogroup in another human patient from Michigan. Convalescent and late convalescent serums from this patient were submitted for viral serology. It appears that infection does occur in our human and animal population with numerous leptospiral serotypes other than *Lept. icterohemorrhagiae, Lept. canicola* and *Lept. pomona,* but their actual prevalence will not be known unless adequate methods for laboratory confirmation are employed.



Hemolytic Anemia in Cirrhosis*

LESLIE ZIEVE, M.D., and EARL HILL, M.D.,† *Minneapolis, Minn.*

That destruction of red cells may occur in hepatic cirrhosis has been recognized for years. The authors' studies have shown there are at least two varieties of the hemolytic process which may occur in this disease.

Introduction

As long ago as 1908, Gauckler[1] described histologic changes in spleens from patients with cirrhosis which he attributed to increased red cell destruction. In 1913 and again in 1920, Eppinger[2,3] offered clinical and laboratory evidence that hemolysis occurs in certain cases of cirrhosis. He was the first to crystallize the association as a definite entity. Fellinger and Klima[4] in 1934 discussed the anemia of cirrhosis in some detail, suspecting hemolysis in a significant number of their patients.

In 1937, Watson[5] presented serial fecal urobilinogen data in 7 jaundiced patients with cirrhosis and hemolytic anemia. All had prominent splenomegaly. The range of the maximal fecal urobilinogen values observed was 320 to 1,257 mg. per day. The range of minimal values observed was 63 to 332 mg. per day. Watson[6] later observed the occurrence of hemolysis in 18% of a small group of cirrhotics. Little was made of these observations and, except for a case reported by Davidson and Fullerton[7] in 1938, nothing further of note appeared in the literature until 1951 when Hyman and Southworth[8] reviewed the association of hemolytic anemia with liver disease, observing 3 women and one girl with cirrhosis who had evidence of vigorous hemolysis. All were probably of the postnecrotic type though, with one exception, data to support this inference were not recorded. Three of the patients had positive Coombs' tests.

With the popularization of red cell studies new interest was awakened in the evidences for hemolysis in a variety of diseases including cirrhosis, and in 1953, Chaplin and Mollison[9] observed a reduced red cell life span in 5 selected patients with advanced cirrhosis. Blood hemoglobin concentration in these patients varied between 9.2 and 11.2 Gm. per 100 ml., and reticulocytes between 2.0 and 5.8 per cent. Splenomegaly was present in 3 of the 5 patients. The average life-span of red cells in these patients, as measured by the Ashby technic, was 25 to 55 days compared to the normal of approximately 120 days. In 1955, Jones and co-workers[10] also reported on a small group of cirrhotics in whom survival studies were performed. Eight of 15 cirrhotics had decreased red cell survival with the Cr^{51} technic, red cell half-lives varying between 15 and 25 days compared to their normal average of 33 days. Splenomegaly was present in 6 of these 8 patients. Also in 1955, Jandl[11] reported detailed hematologic and red cell survival data on 20 selected cases of alcoholic cirrhosis. His represents the most complete work to date. The average Ashby red cell half-life was 23 days with a range of 5 to 49 days (normal 50-70 days). Fecal urobilinogen values, corrected for the degree of anemia, varied between 116 and 1,262 mg. per day with an average of 388 mg. per day. From a plot of the relationship between blood hemoglobin concentration and red cell survival one can estimate crudely that three-fifths of the variation in blood hemoglobin concentration observed in these cirrhotics was accounted for by increased cell destruction and two-fifths by decreased cell production.

It is apparent from these observations that hemolysis occurs more frequently in cirrhosis than was formerly realized. Yet there is still no data available to tell us with reasonable accuracy how often we may expect it. Of even greater moment than this is the paucity of published data that correlates the hemolytic state with the clinical, functional, and anatomic characteristics of the liver disease. For

*Read before the Section on Medicine, Southern Medical Association, Fifty-Second Annual Meeting, New Orleans, La., November 3-6, 1958.

†From the Department of Medicine and the Radioisotope Service, Veterans Administration Hospital, University of Minnesota, Minneapolis, Minn.

TABLE 1

CIRRHOSIS WITH HYPERSPLENISM
General Characteristics

	S1	*S2*	*S3*	*S4*	*S5*
Age, yrs.	51	35	25	53	61
Duration illness, mos.	105	60	40	86	33
Duration hospitalization, mos.	9½	1¼	3½	13½	5¾
Hepatomegaly	MS	MS	A	A	Mi
Splenomegaly	MS	MS	MS	MS	MS
Fever	A	A	A	A	A
Clinical severity	S	Mo	Mo	S	S
Functional severity	S	S	S	S	S
Anatomic severity	S	S	S	S	S
Appetite	F	F	G	Pr	F
Admission wt., lbs.	211	184	157	175	214
Discharge wt., lbs.	200	185	170	135	205
Clinical improvement	Slt	No	No	No	No
Functional improvement	No	Slt	No	No	No
Hematologic improvement	Slt	Slt	No	No	Slt

Abbreviations: MS—moderate or severe, A—absent, Mi—mild, S—severe, Mo—moderate, F—fair, G—good, Pr—poor, Slt—slight, No—none.

illustrative purposes we have assembled such data on 5 relatively unselected cases of the usual variety of cirrhosis with hemolysis as presently generally recognized, the hypersplenic variety.

Cirrhosis with Hypersplenic Hemolytic Anemia

Case summaries. The term hypersplenic applied to the following cases refers to the coexistence of an enlarged spleen and hemolysis, with the spleen playing some role in the hemolytic state, though not necessarily being the only factor nor the most important factor concerned.

Case S1. A 42 year old physician developed epigastric fullness and distress post-prandially 8 years prior to admission. He had imbibed excessively for several years, but carefully pointed out that he had eaten well. Two to four times a month he noticed mild chills and fever, and over a 5 year period he lost 45 lbs. Hepatomegaly and a nonfunctioning gallbladder were first noted 6 years previously. Two years later he was hospitalized with jaundice, hepatosplenomegaly, neutropenia, and thrombocytopenia. Liver biopsy at this time showed portal cirrhosis and several nonspecific granulomas. His clinical status, liver functions, and hematologic picture were not altered by 6 weeks of hospital care.

During a period of hospitalization for an upper respiratory infection 2 years later, esophageal varices were noted. His hepatic abnormalities were essentially

TABLE 2

CIRRHOSIS WITH HYPERSPLENISM
Maximal Abnormalities of Tests

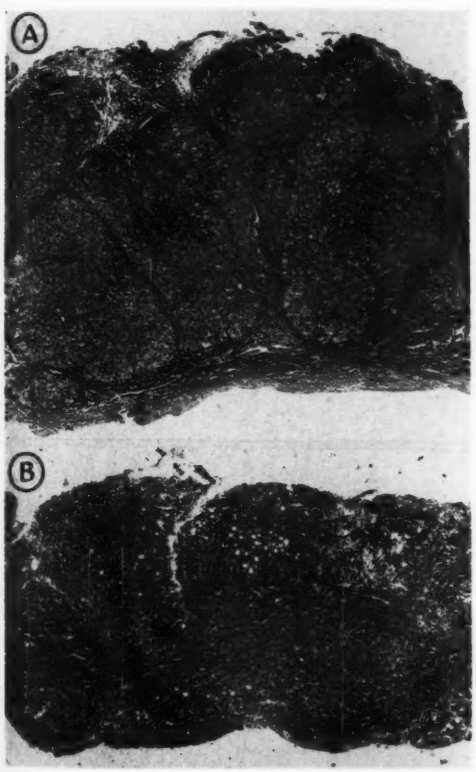
	S1	*S2*	*S3*	*S4*	*S5*
One-minute serum bilirubin, mg.%	2.2	1.4	2.5	3.1	0.9
Total serum bilirubin, mg.%	6.8	6.0	8.7	5.4	4.0
Bilirubin ratio[15]	.32	.23	.29	.57	.23
Total serum cholesterol, mg.%	197	175	250	108	U
Lipemia	A	A	A	A	A
Alkaline phosphatase, K-A units	12	14	22	18	9
Bromsulfalein retention in 45', % BSPc, BSP corrected for jaundice[12]	46c	35c	31c	36c	48
Cephalin flocculation	4+	4+	4+	4+	4+
Prothrombin concentration, %	27	40	18	43	39
Urine urobilinogen, mg./day	128	13	U	U	U
Sedimentation rate, mm./hr.	8	23	9	32	63
Blood hemoglobin, Gm. %	10.1	14.5	9.5	8.0	9.7
Reticulocytes, %	6.9	2.5	6.0	2.9	9.0
Fecal urobilinogen, mg./day	740	460	1350	456	501
Osmotic fragility	Neg	U	Neg	U	U
Spherocytes or Nucleated red cells	A	A	A	P	P
Bone marrow Per cent normoblasts	34	20	47	29	40

Abbreviations: A—absent, P—present, U—unknown.

unchanged. Again that year he was rehospitalized for 7 months. Jaundice, lethargy, edema and ascites, esophageal varices, leukopenia, thrombocytopenia and hemolytic anemia were prominent. Within one week of discharge he was back for another month because of episodes of abnormal behavior, disorientation, semi-stupor and tremulousness. These recurred intermittently thereafter and were attributed to protein and ammonia intoxication. His final admission (Tables 1 and 2) followed in 3 months and he remained in the hospital for 10 more months. An open needle liver biopsy under local anesthesia was obtained (Fig. 1, A) because of some question as to the significance of the previously described granulomas for his present illness. The procedure was tolerated well. Severe portal cirrhosis without granulomas was described. Deterioration was gradual but slowly progressive during the ensuing months and he expired at home several months after leaving the hospital. The total illness lasted approximately 9 years.

Case S2. A 35 year old white machinist who drank excessively was admitted for the third time with anorexia and jaundice. Five years previously his illness began with right upper quadrant abdominal pain followed by progressive anorexia, weight loss, and jaundice. He was first hospitalized one year after the onset

FIG. 1



Liver biopsy sections of cases S1 (A) and S2 (B).

at which time prominent hepatomegaly, spider nevi and peripheral neuritis were observed. The spleen was not palpable. A liver biopsy obtained at this time is shown in figure 1,B. After 2 months of hospitalization and 3 months at home he was re-evaluated. The abnormalities were similar but less marked.

He was next seen 28 months later for hematemesis and melena. Esophageal varices were presumed to be present though not demonstrated in the esophagram. In addition to the previously observed abnormalities of jaundice, hepatomegaly, and collateral abdominal venous channels, he had mild splenomegaly, hemolysis (fecal urobilinogen of 885 mg. per day and reticulocytosis), and the first evidences of diabetes mellitus.

His third admission (Tables 1 and 2) followed the second by one and one-quarter years. Splenomegaly was now prominent, and hemolysis was again present. Leukopenia and thrombocytopenia were evident, but his blood hemoglobin was well maintained. His glucose tolerance was markedly abnormal and he required 50 units of NPH. insulin daily to control his diabetes. His cirrhosis at this time was advanced by clinical and laboratory criteria, and he was discharged after one month with little improvement.

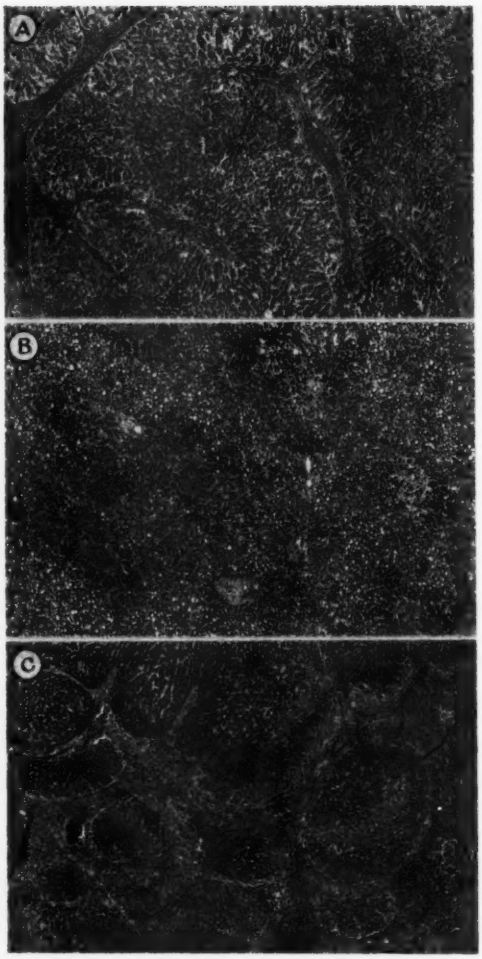
Case S3. A 25 year old gas station attendant, who did not drink, was hospitalized with jaundice, weakness, and fatigue. His illness began 3 years previously with jaundice. Two months later he noted malaise and fever up to 104° F., and a cholecystectomy was performed at his local hospital. Cholecystitis without cholelithiasis was described; however the liver was cirrhotic. He continued to have recurrent episodes of mild jaundice. Three months prior to admission he noted ankle edema followed in a month or two by fever, fatigability, and prominent jaundice. At this examination (Tables 1 and 2) the jaundice was apparent as well as spider nevi, scant hair, splenomegaly, and a slight systolic murmur over the precordium. His liver was not palpable. His heart size was normal on chest x-ray, and no varices were evident on the esophagram. In addition to severe hepatic dysfunction he had leukopenia, thrombocytopenia, and hemolytic anemia. A radioactive chromium red cell survival study showed a half-life of 17 days (normal 25 to 40 days). The patient's subjective sense of well-being belied the objective findings, and he was discharged after failure of various attempts at therapy including steroids for the hemolytic anemia.

Two months following the hospitalization described herein, he was rehospitalized for the last time after a bout of lobar pneumonia. At this time he had diffuse cardiac enlargement in addition to the previous findings. He developed marked fluid retention resistant to diuretics, and expired following the onset of rapid auricular fibrillation. The total illness lasted 44 months. At autopsy his diffusely enlarged heart weighed 480 Gm. and showed patchy fibrosis. The spleen weighed 750 Gm. and the liver 1,160 Gm. Portal cirrhosis of the liver was marked and iron deposition prominent (Fig. 2,A). The pancreas was markedly fibrotic and also contained large amounts of iron.

Case S4. A 53 year old highly intelligent tool and die-maker was transferred to this hospital because of recurrent episodes of protein coma.

Twenty years before admission here he experienced

FIG. 2



Liver autopsy sections of cases S3 (A), S4 (B), and S5 (C).

the first of several hematemeses for which a gastroenterostomy was performed. Five, 10 and 11 years later he had recurrent severe episodes of upper gastrointestinal bleeding for which he was treated symptomatically. After another severe recurrence in 3 years a gastrectomy was performed, at which time an enlarged liver and spleen were seen and a liver biopsy showed portal cirrhosis. Three years following the gastrectomy he had two recurrences of hematemesis and an effective portacaval shunt was performed. This was 17 years after the first episode of bleeding. Liver biopsy again showed cirrhosis.

One year after the shunt procedure he was rehospitalized with hemolytic anemia and leukopenia. He had had episodes of tremulousness, somnolence, and unsteadiness. In the hospital three episodes of psychotic behavior and tremulousness were precipitated by protein diets of 40 or more Gm. In each instance improvement followed protein restriction to less than 25 Gm. A recurrent episode of deep coma followed excessive protein consumption several months later. Paralysis of both legs was evident after recovery. He was subsequently restricted to a daily protein intake of 20 to 35 Gm., but he still had recurrent episodes of tremulousness, confusion, and aberrant behavior.

Seven months after the severe coma and onset of paralysis he was transferred to this hospital. He was alert on admission. His liver was not palpable, though splenomegaly, ascites, and edema were prominent, as was a spastic paraplegia. His hepatic abnormality was unchanged and his hemolytic anemia persisted (Tables 1 and 2). He seemed to tolerate 30 Gm. of protein for several weeks, so an attempt was made to increase his protein intake with disastrous results as soon as 50 Gm. per day was exceeded. He lapsed rather abruptly into deep coma which responded within 24 hours to 75 Gm. of arginine hydrochloride. Thereafter he was only able to tolerate 25 Gm. of protein daily. Despite this marked restriction he had approximately 13 episodes of confusion, stupor, or coma over the next 13 months. These responded dramatically to 50 to 100 Gm. of arginine hydrochloride or arginine-glutamate intravenously. In one year he received a total of 1,375 Gm. of arginine intravenously. The amino-acid seemed specific for his episodes of protein coma. However his course was steadily downhill with wasting as he lost his stores of body protein. He died in an episode of coma which did not respond to 350 Gm. of arginine-glutamate.

Postmortem examination revealed an acute stomal ulcer with perforation and generalized peritonitis as the immediate cause of death. Marked hemosiderosis was present in the liver and pancreas, and the latter was fibrotic. The liver weighed 950 Gm. and showed portal cirrhosis and fatty metamorphosis in addition to hemosiderosis (Fig. 2,B). The spleen weighed 560 Gm. The portacaval shunt was patent. Alzheimer type II glial cells were prominent in the brain, and the direct and crossed pyramidal tracts were demyelinated.

Case S5. A 61 year old chronic alcoholic was hospitalized for the third time because of anorexia, ascites, lethargy, and episodes of confusion and stupor. His illness began 26 months previously with weakness, jaundice and abdominal swelling. One month after onset he was hospitalized locally where two paracenteses were performed before transfer to this institution. He had lost about 50 lbs. since his illness began. Massive ascites and edema were again evident. Numerous spider nevi were present, and he was jaundiced. Hepatic dysfunction was marked. Anemia and thrombocytopenia were present, and his cuff test was positive. He improved somewhat during 2 months of hospitalization.

Five months after discharge he was readmitted for weakness, ascites, edema, and a leg ulcer. Slight improvement resulted from a low sodium diet, though his hepatic status was essentially unchanged after 4 months of care.

His third hospitalization, summarized herein (Tables 1 and 2) followed the second by approximately one year. On admission he was disoriented for time and place. Ascites was marked, as was his hepatic dysfunc-

tion. Hemolytic anemia and thrombocytopenia were prominent and he had a bleeding tendency. After two paracenteses and an episode of bleeding from the abdominal puncture wound, he gradually lapsed into hepatic coma from which he recovered following 50 Gm. of potassium glutamate intravenously. He continued severely decompensated, though his ascites improved somewhat over a period of several months, and his leg ulcer gradually healed. He was discharged after almost 6 months of hospital care only to return in one month for the last time.

His massive ascites and edema had recurred and he was confused and disoriented. Somnolence continued prominently and he lapsed intermittently into a semistuporous state, though having intervals of lucidity. Seven weeks after admission he developed abdominal distress and vomiting, lapsed into deep hepatic coma and died within 4 days. At autopsy dark bloody fluid was found in the entire gastrointestinal tract. Superficial esophageal erosions in the area of varicosities were suspected to be the source. The liver weighed 1,300 Gm. and was markedly cirrhotic (Fig. 2,C). The spleen weighed 500 Gm. The final diagnoses were portal cirrhosis, esophagitis and esophageal varices with bleeding, and hepatic coma.

Clinical data. Pertinent information is summarized in table 1. The ages of these patients ranged between 25 and 61 years. The illnesses were prolonged lasting 33 to 105 months. Hospitalization was also prolonged. Liver size was variable, sometimes being large and others small. Prominent splenomegaly occurred in each patient. Fever was absent. The patient's appetite was usually fair or poor, and the weight changes between admission and discharge corresponded. The good appetite of patient S3 belied the state of his health. He deteriorated progressively and died a few months later.

The clinical, functional, and anatomic abnormality in these patients was moderately severe or severe, generally the latter. There was also little or no improvement in the clinical, functional, and hematologic findings during the course of hospitalization.

Laboratory data. The maximal abnormalities observed with various tests are given in table 2. Jaundice was mild to moderate, the total serum bilirubin concentration varying between 4.0 and 8.7 mg. per 100 ml. at its worst. The ratio of the direct reacting one-minute bilirubin to the total bilirubin concentration, called the bilirubin ratio, was usually low, varying between 0.23 and 0.57. This disproportionate increase in the indirect-reacting fraction is consistent with the existence of a chronic hemolytic process. Serum cholesterol concentration was normal or low, and lipemia was absent. The alkaline phosphatase was normal or slightly elevated ranging between 9 and 22 King-Armstrong units. Bromsulfalein retention was severe even after adjusting for the degree of jaundice present,[12] and the cephalin flocculation test was markedly abnormal. Prothrombin concentration was generally low and unresponsive to vitamin K.

The sedimentation rate was appreciably elevated in but one patient. Anemia was moderate, blood hemoglobin concentration varying between 8.0 and 14.5 Gm. per 100 ml. Reticulocytosis was not high, values of 2.5 to 9.0% being observed. Fecal urobilinogen excretion ranged between 456 and 1,350 mg. per day. Osmotic fragility was normal in the two patients with studies. Nucleated red cells were not described in the routine blood smear of these patients, though spherocytes were noted in two instances. Bone marrow hyperplasia was present but not vigorous, normoblasts varying between 20 and 47% of bone marrow cells.

These data portray patients with severe hepatic dysfunction who have a chronic persistent hemolytic state with a significant, though not vigorous, bone marrow reaction.

Comment. Though these patients illustrate very well the usual variety of cirrhosis with hypersplenic hemolytic anemia, many variations on this theme may be seen, and we are confident there is much to be learned yet from a careful review of a large number of such patients.

However, there is an entirely different variety of hemolytic anemia in cirrhosis which has only recently been recognized and which we have called hyperlipemic hemolytic anemia. The patients present the triad of jaundice, hyperlipemia, and hemolytic anemia. Cirrhosis is generally not prominent, and fatty infiltration is probably an essential ingredient. A discussion of this syndrome has been published[13] and will not be repeated here. Review of this paper is essential to a complete understanding of the data that follow. To contrast this hyperlipemic hemolytic syndrome with the hypersplenic variety, the clinical and laboratory data of the 5 most complete cases have been assembled as before.

Cirrhosis with Hyperlipemic Hemolytic Anemia

Case summaries. Reference thirteen gives

TABLE 3

CIRRHOSIS WITH HYPERLIPEMIA
General Characteristics

	L1	*L2*	*L3*	*L4*	*L5*
Age, yrs.	35	39	48	59	37
Duration illness, mos.	2¾	1½	2	2	1¾
Duration hospitalization, mos.	1¾	2	1¾	1½	1
Hepatomegaly	MS	MS	MS	MS	MS
Splenomegaly	Mi	A	A	A	A
Fever	4 wks.	6 wks.	3 wks.	4 wks.	2 wks.
Clinical severity	Mi	Mi	Mi	Mi	Mi
Functional severity	Mi	Mi	Mi	Mi	Mo
Anatomic severity	Mi	Mi	Mi	U	Mo
Appetite	G	G	G	G	G
Admission wt., lbs.	128	112	170	86	184
Discharge wt., lbs.	147	132	176	106	178
Clinical improvement	Mkd	Mkd	Mkd	Mkd	Mkd
Functional improvement	Mkd	Mkd	Sgn	Mkd	Mkd
Hematologic improvement	Mkd	Mkd	Mkd	Mkd	Mkd

Abbreviations: MS—moderate or severe, Mi—mild, A—absent, Mo—moderate, U—unknown, G—good, Mkd—marked, Sgn—significant.

detailed histories and pathologic data on the five patients being considered. The term hyperlipemic refers to the coexistence of elevated serum lipids and hemolysis, with the implication that the abnormality of serum lipids (or an abnormal lipid) plays some role in the hemolytic state.

Clinical data. These are summarized in table 3. The age range of the patients was 35 to 59 years. Their illnesses were brief, generally about 2 months, and hospitalization was not prolonged. Enlargement of the liver was uniformly moderate or severe shortly after admission though shrinkage toward normal was rapid as the patient improved. The spleen was usually not palpable, and if felt was only slightly enlarged. A low-grade fever lasting several weeks was the rule. The patient's appetite was invariably good. The clinical, functional, and anatomic abnormality was generally, though not invariably, mild to start with, and the improvement in the clinical, functional, and hematologic findings after hospitalization was typically marked.

Laboratory data. Maximal abnormalities observed with the various tests are listed in table 4. Jaundice was generally moderate or severe, but the bilirubin ratio was not de-

TABLE 4

CIRRHOSIS WITH HYPERLIPEMIA
Maximal Abnormalities of Tests

	L1	*L2*	*L3*	*L4*	*L5*
One-minute serum bilirubin, mg. %	1.8	5.8	3.8	10.0	3.3
Total serum bilirubin, mg. %	2.2	9.6	5.9	20.0	5.5
Bilirubin ratio	.82	.60	.64	.50	.60
Total serum cholesterol, mg. %	656	538	394	501	335
Lipemia	U	P	P	P	A
Alkaline phosphatase, K-A units	7	68	17	25	11
Bromsulfalein retention in 45′, % BSPc, BSP corrected for jaundice[12]	5c	15c	11	10c	18c
Cephalin flocculation	1+	0	0	2+	3+
Prothrombin concentration, %	70	100	100	47	50
Urine urobilinogen, mg./day	0.4	2.8	U	7.8	136
Sedimentation rate, mm./hr.	85	75	92	113	37
Blood hemoglobin, Gm. %	9.5	8.3	11.1	10.0	9.4
Reticulocytes, %	7.9	7.8	10.9	16.9	13.7
Fecal urobilinogen, mg./day	252	276	514	440	249
Osmotic fragility	+	±	+	+	+
Spherocytes or Nucleated red cells	P	P	P	P	P
Bone marrow Per cent normoblasts	58	64	53	U	50+

Abbreviations: U—unknown, P—present, A—absent.

creased. In none of 15 similar patients was this ratio decreased, and the highest total serum bilirubin concentration observed was 43 mg. per 100 ml., indicating that rather severe jaundice may occur.

Serum cholesterol levels were high, varying between 335 and 656 mg. per 100 ml. The highest cholesterol value observed among 20 such patients studied was 1,117 mg. per 100 ml. Frank lipemia was present in 3 of these 5 patients, and in one-half of the larger group of twenty. We suspect it may have been present in almost every case at some maximal point in the illness.

Alkaline phosphatase values were normal or slightly elevated with one exception in which a value of 68 King-Armstrong units was recorded. This high value in combination with fever, acute jaundice, hypercholesterolemia, and the negative flocculation reaction led to a suspicion of obstructive jaundice and surgical exploration for a common duct stone which was not found. Bromsulfalein retention was mild, and the cephalin flocculation normal or incomplete as a rule. The 3+ flocculation of the fifth patient rapidly returned to normal. Prothrombin concentrations were normal or slightly decreased. Urine urobilinogen values were quite variable, in one instance being very high at the time of admission.

Erythrocyte sedimentation was generally markedly increased, values up to 113 mm. per hour being observed. These elevated values gradually returned to normal over a period of several weeks as the patients improved. The anemia was moderate, hemoglobin concentrations varying between 8.3 and 11.1 Gm. per 100 ml. Reticulocytosis was generally vigorous, values of 7.8 to 16.9% being recorded. Fecal urobilinogen excretion varied between 249 and 514 mg. per day. Osmotic fragilities were generally positive, and spherocytes or nucleated red cells were frequently described in the initial routine blood smears. Bone marrow erythroid hyperplasia was marked, normoblasts exceeding 50% of the marrow cells as a rule.

We did not have direct measurements of red cell destruction utilizing labeled cells in these patients. However, Holt and Korst[14] have reported Cr^{51} red cell survival data in five similar cases. The red cell half-lives varied from 10 to 17 days compared to their normal of 28 to 32 days, a reduction of 50% on the average. In a recent similar patient whom we have studied, the Cr^{51} survival curve during the first 10 days yielded a half-life of 8 days, indicating vigorous red cell destruction. Simultaneously the osmotic fragility of this patient's red cells was markedly increased.

The foregoing data portray patients with jaundice, hyperlipemia or hypercholesterolemia, mild hepatic dysfunction, and acute transient hemolytic anemia with increased fragility of red cells and a vigorous hyperplastic bone marrow response.

Hypersplenic and Hyperlipemic Cases Contrasted

The specific differences between the two types of cases are now readily apparent as

TABLE 5

GENERAL CHARACTERISTICS

	Hypersplenism		*Hyperlipemia*	
	Mean	*Range*	*Mean*	*Range*
Age, yrs.	45	25-61	44	35-59
Duration illness, mos.	65	33-105	2	1½-2¾
Duration hospitalization, mos.	6¾	1¼-13½	1½	1-2
Hepatomegaly	MS	in 2 of 5	MS	in 5 of 5
Splenomegaly	MS	in 5 of 5	A	in 4 of 5
Fever	A	in 5 of 5	P	in 5 of 5
Clinical severity	MS	in 5 of 5	Mi	in 5 of 5
Functional severity	S	in 5 of 5	Mi	in 4 of 5
Anatomic severity	S	in 5 of 5	Mi	in 3 of 4
Appetite	G	in 1 of 5	G	in 5 of 5
Admission wt., lbs.	188	157-214	136	86-184
Discharge wt., lbs.	179	135-205	148	106-178
Clinical improvement	NSgn	in 5 of 5	Sgn	in 5 of 5
Functional improvement	NSgn	in 5 of 5	Sgn	in 5 of 5
Hematologic improvement	NSgn	in 5 of 5	Sgn	in 5 of 5

Abbreviations: MS—moderate or severe, A—absent, P—present, Mi—mild, S—severe, G—good, NSgn—not significant, Sgn—significant.

TABLE 6

MAXIMAL ABNORMALITIES OF TESTS

	Hypersplenism		*Hyperlipemia*	
	Mean	*Range*	*Mean*	*Range*
One-minute serum bilirubin, mg. %	2.0	0.9-3.1	4.9	1.8-10.0
Total serum bilirubin, mg. %	6.2	4.0-8.7	8.6	2.2-20.0
Bilirubin ratio	.33	.23-.57	.63	.50-.82
Total serum cholesterol, mg. %	183	108-250	485	335-656
Lipemia	A	in 5 of 5	P	in 3 of 4
Alkaline phosphatase, K-A units	15	9-22	26	7-68
Bromsulfalein retention in 45', % BSPc, BSP corrected for jaundice[12]	39	31-48	12	5-18
Cephalin flocculation	4+	All 4+	1+	0-3+
Prothrombin concentration, %	33	18-43	73	47-100
Urine urobilinogen, mg./day	71	13-128	29	0.4-136
Sedimentation rate, mm./hr.	27	8-63	80	37-113
Blood hemoglobin, Gm. %	10.4	8.0-14.5	9.7	8.3-11.1
Reticulocytes, %	5.5	2.5-9.0	11.4	7.8-16.9
Fecal urobilinogen, mg./day	702	456-1350	346	249-514
Osmotic fragility	Neg	in 2 of 2	Pos	in 4 of 5
Spherocytes or Nucleated red cells	P	in 2 of 5	P	in 5 of 5
Bone marrow Per cent normoblasts	34	20-47	56	50-64

Abbreviations: A—absent, P—present.

summarized in the comparisons of tables 5 and 6.

Clinical data. The illnesses of the hypersplenic cases were prolonged as were the periods of hospitalization, in contrast to the hyperlipemic patients whose illnesses were acute and brief. Prominent hepatomegaly was more typical of the hyperlipemic cases, and splenic enlargement by contrast uncommon. Low-grade fever persisting for several weeks was typical of the hyperlipemic cases only. These patients invariably had good appetites, sometimes eating voraciously. This was reflected in the weight gain during the period of hospitalization. In contrast, the hypersplenic cases did not eat well and lost weight.

The liver disease in the hypersplenic cases was severe, clinically, functionally, and anatomically. By contrast the liver disease in the hyperlipemic cases was typically mild. Correspondingly there was little or no improvement with hospitalization in the clinical, functional, and hematological parameters of the patients with hypersplenism and marked improvement in those of the patients with hyperlipemia.

Laboratory data. Jaundice tended to be more severe among the hyperlipemia patients, though the bilirubin ratio, reflecting the relative amounts of direct and indirect reacting pigment, was not decreased as it was in the hypersplenic cases. Hyperlipemia and hypercholesterolemia did not occur in the hypersplenic cases in whom liver dysfunction was more striking and more persistent. A brisk rise in erythrocyte sedimentation was more characteristic of the hyperlipemia patients. The degree of anemia was essentially similar in the two types of cases. However, the reticulocyte response was greater in the hyperlipemia patients, while fecal urobilinogen excretion was greater in the hypersplenic patients. Increased osmotic fragility of red cells and the presence of spherocytes and nucleated red cells in routine peripheral blood smears was common in the hyperlipemia but not the hypersplenic cases. Similarly the bone marrow response was more vigorous in the hyperlipemic cases.

Comment. The differences between these two types of cases are so striking one is predisposed to place them in entirely different categories. The mechanisms of hemolysis are very likely entirely different. Yet we think these cases fit at opposite poles of a continuous spectrum of variations with respect to their liver disease. On the one hand the hyperlipemic cases typically have mild hepatic changes which are easily reversible. In terms of the cirrhotic process they are in the incipient or earliest stages. During this phase of the disease the vigorous mobilization of lipid leading to hyperlipemia and its hemolytic effects on red cells is possible. This is also easily reversible. With time and repeated

similar episodes progressive cirrhosis develops, and the responsiveness to abstinence and a nutritious diet decreases. Accumulation of fat within the liver and mobilization of lipid from the liver or fat depots becomes less prominent. Portal hypertension and splenomegaly develop, generally over a prolonged interval of time. During this period the tendency is toward hypolipemia rather than hyperlipemia. Eventually the cirrhosis becomes advanced. A hypersplenic phase may supervene along the way, again resulting in hemolysis of red cells, this time by a process which tends to be unremitting and persistent.

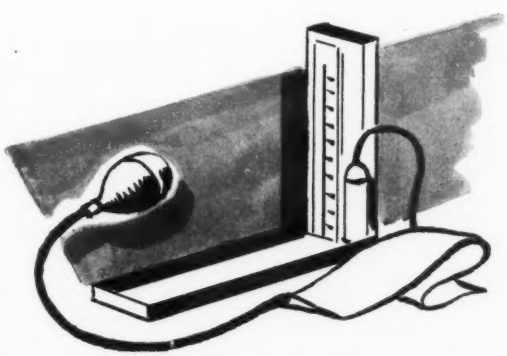
It is quite apparent even with this simplified hypothetical sequence that many variations along such a spectrum are possible because of a host of factors that can influence progression or healing. Even within each of the two groups described in some detail herein, and not considering the intervening spectrum of possibilities, the variations among cases can be quite striking and must be clarified by observations on large samples. A study of the variations and the incomplete cases in sufficient numbers, should further our understanding of both the incidence and the mechanisms of hemolysis in cirrhosis.

Conclusion

By way of recapitulation it seems clear that there is much to learn regarding hemolytic anemias that occur in cirrhosis. We suspect some degree of hemolysis is quite common. Ultimately we may come to distinguish a spectrum of variations in the hemolytic state depending upon variations in the cirrhotic process and interactions among various etiological mechanisms involved. Today we can at least distinguish two varieties of hemolysis in cirrhosis. These are strikingly different, one acute, the other chronic, and apparently arise by entirely different mechanisms.

References

1. Gauckler, E.: Les modalites histologiques de l'hematolyse et le role de la rate dans l'evolution du pigment sanguin, Arch. mal. coeur 1:401, 1908.
2. Eppinger, H.: Zur Pathologie der Milzfunktion, Berl. klin. Wchnschr. 50:1509, 1913.
3. Eppinger, H.: Die hepatolienalen Erkrankungen. Berlin, Julius Springer, 1920.
4. Fellinger, K., and Klima, R.: Lebercirrhose und Anamien, Ztschr. klin. Med. 126:547, 1934.
5. Watson, C. J.: Studies of Urobilinogen. III. The Per Diem Excretion of Urobilinogen in the Common Forms of Jaundice and Disease of the Liver, Arch. Int. Med. 59:206, 1937.
6. Watson, C. J.: Hemolytic Jaundice and Macrocytic Hemolytic Anemia: Certain Observations in a Series of 35 Cases, Ann. Int. Med. 12:1782, 1939.
7. Davidson, L. S. P., and Fullerton, H. W.: Some Rare Types of Macrocytic Anemia, Quart. J. Med. 7:43, 1938.
8. Hyman, G. A., and Southworth, H.: Hemolytic Anemia Associated With Liver Disease, Am. J. M. Sc. 221:448, 1951.
9. Chaplin, H., and Mollison, P. L.: Red Cell Life-Span in Nephritis and in Hepatic Cirrhosis, Clin. Sc. 12:351, 1953.
10. Jones, P. N., Weinstein, I. M., Ettinger, R. H., and Capps, R. B.: Decreased Red Cell Survival Associated With Liver Disease, A.M.A. Arch. Int. Med. 95:93, 1955.
11. Jandl, J. H.: The Anemia of Liver Disease: Observations on its Mechanism, J. Clin. Invest. 34:390, 1955.
12. Zieve, L., Hanson, M., and Hill, E.: Studies of Liver Function Tests. II. Derivation of a Correction Allowing Use of the Bromsulfalein Test in Jaundiced Patients, J. Lab. & Clin. Med. 37:40, 1951.
13. Zieve, L.: Jaundice, Hyperlipemia, and Hemolytic Anemia: A Heretofore Unrecognized Syndrome Associated With Alcoholic Fatty Liver and Cirrhosis, Ann. Int. Med. 48: 471, 1958.
14. Holt, F. J., and Korst, D. R.: Transient Hemolytic Anemia Associated with Liver Disease, Clin. Res. 6:392, 1958.
15. Zieve, L., Hill, E., Hanson, M., Falcone, A. B., and Watson, C. J.: Normal and Abnormal Variations and Clinical Significance of the One-Minute and Total Serum Bilirubin Determinations, J. Lab. & Clin. Med. 38:446, 1951.



CASE REPORT

Acute Pulmonary Histoplasmosis*

GLENN E. HORTON, M.D., JOHN C. LARKIN, M.D., and SAMUEL PHILLIPS, M.D.,† *Memphis, Tenn.*

This case report points up the important features of pulmonary histoplasmosis.

ACUTE PULMONARY HISTOPLASMOSIS has masqueraded as "cave sickness," "acute miliary pneumonitis," as well as other titles in the literature before it was established to be the acute phase of an infectious disease caused by a fungus, *Histoplasma capsulatum*.[1] This disease, however, continues to pose a problem in recognition, diagnosis, and management. The purpose of this paper is to present a case report illustrating the clinical features of an unusually severe acute form of the disease, with a review of the pertinent literature, the various differential features, the diagnostic procedures that were utilized, and the management employed.

Review of the Literature

Historical background. The initial recognition of the infecting organism was made by Darling[2] in Panama, in 1906, after necropsy of a 27 year old Martininquan Negro who had "pseudo-tubercles in the lungs" and focal necrosis in the spleen, liver and lymph nodes. Large mononuclear cells within these visceral organs were observed which Darling considered analogous to swollen "histo" cytes containing "plasmo" dium-like encapsulated organisms. Hence he coined the name for the organism, *"Histoplasma capsulatum,"* and for the disease, "Histoplasmosis." He believed the disease to be a protozoan infection similar to kala-azar. From 1924 to 1934, further work by other observers[3] finally led to the positive identification of the organism as a fungus by DeMonbreun,[4] which he made conclusive by the fulfillment of all of Koch's postulates.

Watson and Riley,[5] reported the first case in North America in 1926. By 1950, 123 cases had been reported, many of them single cases with autopsy reports.[6] Most of these early reports considered histoplasmosis to be a rare, uniformly fatal disease. But by the early 1940's, it was beginning to be suspected that the disease might be more wide-spread and less uniformly fatal, mainly as a result of findings arising from the general mobilization for World War II, in which it was found that the chest x-rays of many tuberculin-negative inductees demonstrated intrathoracic calcifications.[7] In 1945 Christie and Peterson,[8] as well as Palmer,[9] reported that there was a high incidence of pulmonary calcification in nonreactors to tuberculin among residents in the Mississippi Valley area. They also noted that these individuals were sensitive to histoplasmin, a fact which has been confirmed by numerous subsequent studies. By 1950, it had become apparent to most informed observers that the majority of those infected with *H. capsulatum* had no clinical symptoms.[10] The evidence of previous infections was taken to be a positive histoplasmin skin test, often supported by a chest x-ray film which revealed calcific densities in the lung or hilar areas. More recently, studies of epidemics arising from exposure to dust from barns, storm cellars, caves, chicken houses, silos, etc., have established definite proof that primary infections with *H. capsulatum* also may produce definite clinical symptoms.[1,11]

Geographic distribution and epidemiology. Based on the evidence obtained by studies of skin sensitivity[12] there appears to be a

*Read before the Section on Medicine, Southern Medical Association, Fifty-Second Annual Meeting, New Orleans, La., November 3-6, 1958.

†From the Pulmonary Disease Service, Veterans Administration Medical Teaching Group Hospital (Kennedy), Memphis, Tenn.

spotty but world-wide distribution of histoplasmosis. People in Mexico and Central American countries have a relatively high sensitivity rate. Brazil and Argentina in South America show high rates, while countries in Africa show a low and scattered incidence. The incidence is low in far Eastern Europe. In Italy, the rate appears to be a little higher. The area of greatest endemicity appears to be in the Southern and Middle Western States.[8-11] This area includes the states of Tennessee, Kentucky, Missouri, Iowa, Kansas, Arkansas, Louisiana, Illinois, Ohio and Indiana. Sensitivity falls off in all directions from this area known as the Mississippi and Ohio River valleys.

Histoplasmosis has been determined to be primarily a pulmonary infection caused by inhalation of the fungus from an exogenous source in nature. *Histoplasma* was first cultured from soil specimens by Emmons[13] in 1948. In a study of epidemics of histoplasmosis, most were related to excavations or dust exposure in closed areas contaminated by pigeon or chicken excreta, and in some of these epidemics, the fungus was isolated from the suspected soil, in 16% of 137 samples studied.[1] Chicken houses produced the highest yield, although many of them had long been abandoned. The fungus also has been isolated from many wild and domestic animals; there are no reported cases of transmission of this infection from animal to man. There have been no reported cases of transmission from man to man.

There are several classifications proposed in the literature. The following classification was suggested by the Veterans Administration in 1957.[14]

A. Acute (subacute) pulmonary histoplasmosis,
   1. Asymptomatic
   2. Symptomatic
B. Chronic pulmonary histoplasmosis
C. Disseminated histoplasmosis,
   1. Generalized (progressive)
   2. Localized (specify lesion and site)
D. Residual lesions of histoplasmosis,
   1. Histoplasmosis, calcified miliary nodules
   2. Histoplasmosis, calcified nodules (specify site)

The category in which this case report would fit would be acute pulmonary histoplasmosis, symptomatic type.

Case Report

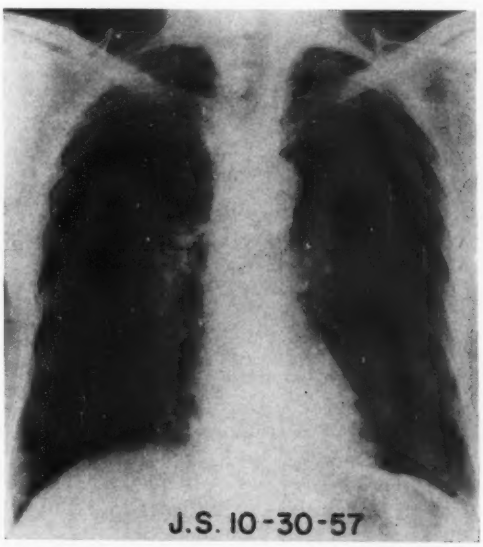
J. S., a 55 year old white male tent rental salesman, was admitted to the Veterans Administration Teaching Group (Kennedy) Hospital on Oct. 30, 1957, with a history of an acute shaking chill 5 weeks prior to admission, followed by daily fever, a 30 lb. weight loss, malaise, and a cough with but little sputum production. His wife supposedly had similar symptoms beginning approximately 2 weeks before he became ill.

He had no gastrointestinal or genitourinary symptoms. The last roentgenogram of his chest was made in 1941 and was supposed to have been negative. He gave no history of exposure to chicken or other avian manure. However, the patient's activity as a tent rental salesman required him to travel about, setting up tents for various shows of live stock. He was similarly involved in carnivals, exhibits, evangelical meetings, but never in the exhibition of fowl. In June 1957, he had handled tents with which pigeons had been in obvious contact. The patient was not aware of any exposure to chicken manure.

Physical examination. On admission this patient was acutely ill with a temperature of 103° F., a pulse of 100, and B.P. of 112/82. He weighed 120 lbs. representing approximately a 30 lb. weight loss. The chest was thin and symmetrical. Fine moist rales were scattered throughout both lower lung fields but no friction rubs were found. The abdomen was soft and the liver and spleen were not palpable. There was no evidence of generalized or local adenopathy.

Laboratory. The chest film on admission (Fig. 1) showed diffuse granular infiltrations throughout the lower two-thirds of both lungs. Subsequent chest films are shown in figures 2 and 3. On admission, all sputa, gastric smears and cultures were negative for acid-fast bacilli and pathogenic fungi. Repeated PPD skin tests were negative. Bone marrow cultures were

FIG. 1

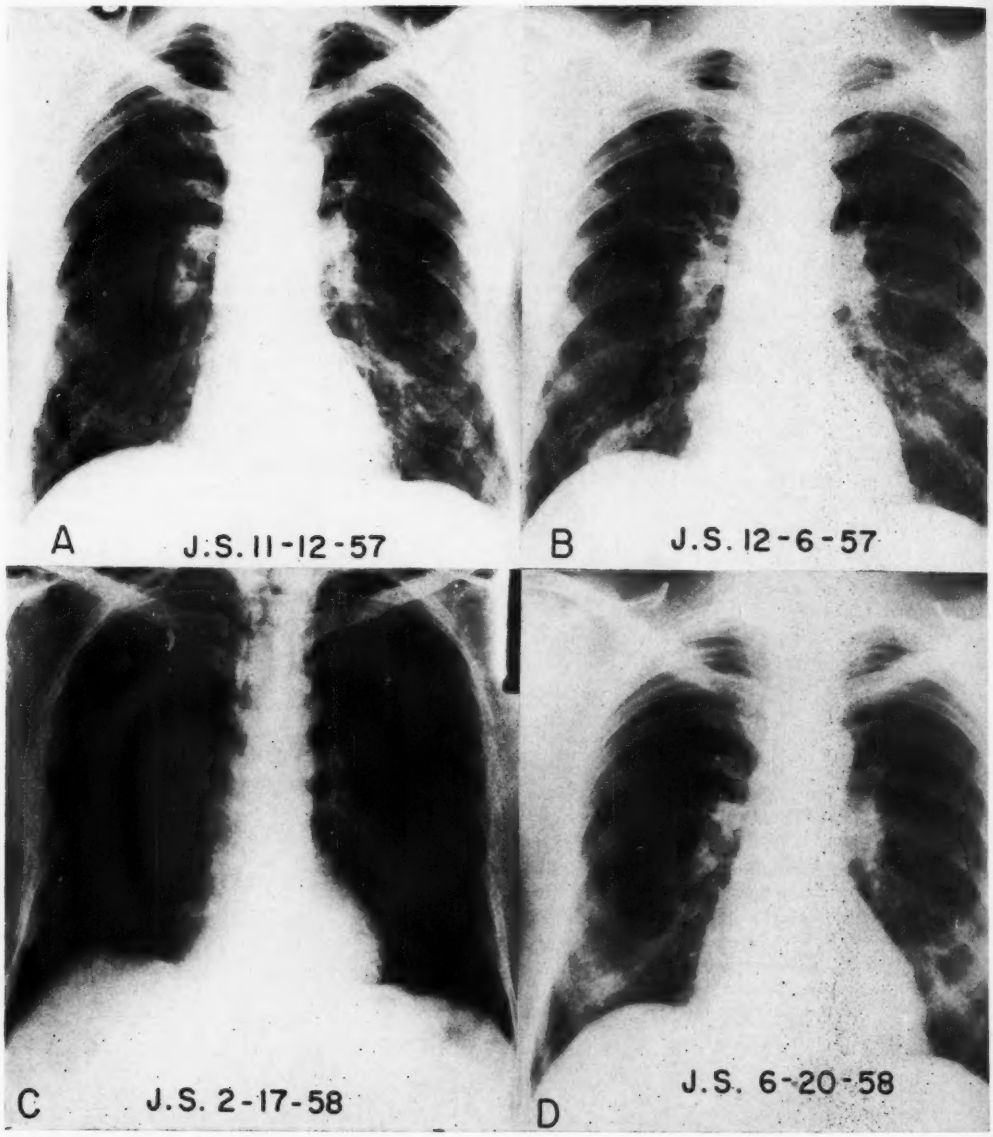


Admission roentgenogram shows diffuse granular infiltrations throughout the lower two-thirds of both lungs with enlargement of both hilar shadows.

negative for acid-fast organisms and fungi. The histoplasmin skin test was positive. The initial serologic test for histoplasmosis was negative but subsequently became positive as indicated in table 1. A biopsy of a supraclavicular scalene node revealed microscopic findings similar to that of sarcoid (Fig. 4), but the culture of the nodes revealed the presence of *Histoplasma capsulatum* (Fig. 5). Other laboratory data include an admission white blood count of 19,000 with 86% neutrophils. This subsequently became normal.

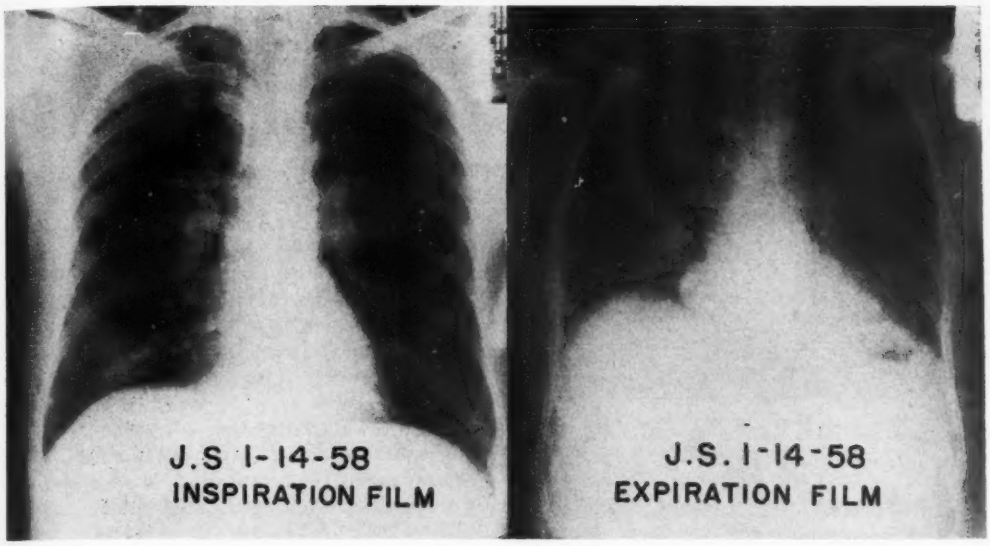
Hospital course. The patient was first admitted to the General Medical Service, with a T. of 103°, and was acutely ill. Acute miliary tuberculosis was suspected and the patient was transferred to the Pulmonary Disease Service, after treatment with INH,

FIG. 2



(A) Considerable clearing of pulmonary infiltrations with some residual at right base and regression of hilar enlargement to almost normal. (B) Persistence of right basilar infiltration and increase of right hilar shadow. (C) Decrease of infiltration at right base and regression of right hilar enlargement. (D) Last available chest roentgenogram.

FIG. 3



Expiration film accentuates the appearance of the infiltration to the right base as compared to the inspiration film.

PAS and streptomycin was begun. These were discontinued when the cultures for tubercle bacilli were reported negative. In view of the positive skin test to histoplasmin, a negative Mantoux test with PPD No. 2, and the subsequent rise in the serologic titer, a diagnosis of acute pulmonary histoplasmosis was made. On bedrest the patient became afebrile on the fifth hospital day, and felt sufficiently well before the end of one month to ask for a pass, which was granted. He went hunting and admittedly over-exerted himself. He experienced a return of malaise, and when he came back to this hospital he again had fever. At this point he agreed to the scalene node biopsy which revealed the findings already described. The patient became afebrile again on bedrest, and showed improvement on serial x-ray studies of the chest. The subsequent serologic findings are presented in table 1.

Since the patient lived near Kansas City, Missouri, he was transferred to the Kansas City VA Hospital on Mar. 31, 1958, and entered under the care of Dr. Charles E. Andrews. He remained relatively asymptomatic. Pulmonary function studies were carried out and revealed a total vital capacity of 4.24 liters (121% of predicted) with a timed vital capacity of 84% in the first second. The residual volume to total lung capacity ratio was 15 per cent. The patient was discharged from that hospital asymptomatic on May 22, 1958. Following his discharge, he returned to work, but noticed increased cough and sputum. He refused to be re-hospitalized, although he was recalled twice. The last follow-up visit was on June 20, 1958.

Amphotericin-B therapy had been considered for this patient, but due to his inability to remain in the hospital for a sufficient period of time, as well as the questionable need, it was not administered.

TABLE 1

CASE J.S. SEROLOGICAL FINDINGS IN ACUTE PULMONARY HISTOPLASMOSIS
(VALUES ARE RECIPROCALS OF TITER)
ACUTE PULMONARY HISTOPLASMOSIS

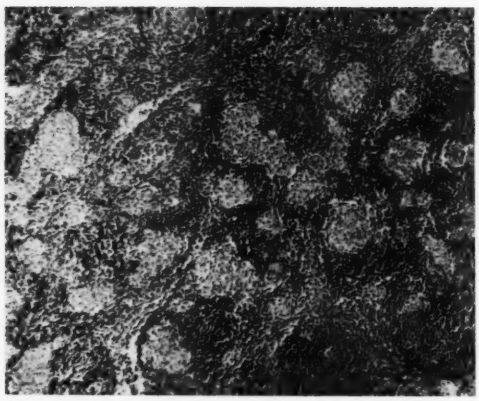
	Serological Tests with H. Capsulatum Antigens		
	Complement Fixation		*Hemagglutination*
Date	*Whole Yeast Antigen*	*Mycelial Antigen*	*Mycelial Antigen*
10-30-57	0	0	
11-12	16	0	32
11-22	8	0	32
12- 3	8	0	8
1-29-58	16	0	
2-12	8	0	
4- 1	16	0	0
5-22	16	0	0

Discussion

What is the importance to the practicing clinician of recognizing histoplasmosis? The reasons are multifold.

Differential diagnosis. Histoplasmosis is an ubiquitous disease, the organism often elusive to our methods of identification, and it must be considered in the differential diagnosis of many acute and chronic infections.[15] It may, in the acute form, as in this case, clinically simulate miliary tuberculosis, other acute respiratory diseases of viral or bacterial origin such as viral pneumonia, other mycotic infections, other forms of tuberculosis, and fevers of undetermined origin.

FIG. 4



Photomicrograph of biopsy specimen from right scalene lymph node. Sarcoid-like histologic appearance with nodular aggregates of epithelioid cells and occasional giant cell without necrosis. (H & E stain X 60.)

In the chronic form, it may and often does mimic chronic tuberculosis, both clinically and radiographically.[16]

The so-called "healed," but not yet calcified, histoplasma granulomas may simulate primary or metastatic neoplasm, lymphomas, leukemia and sarcoid. It is now generally believed that miliary calcifications, symmetrical in appearance and distribution, represent a residual of "healed" histoplasma infection rather than quiescent tuberculosis.

Complications. Even though the portal of entry is the respiratory tract,[15] many organs other than the lungs may become the foci of infection with *H. capsulatum*. This is particularly true in the disseminated form, especially in infants, where the infectious disease can produce enlargement of the liver, spleen and lymph nodes, simulating leukemia or lymphoma. Meningitis may be a complication. The organism has been found in skin ulcerations, and in mucosal lesions of the mouth, tongue, pharynx, larynx, gastrointestinal tract, penis, and anus. Some of these lesions have simulated cancer on gross appearance. Histoplasmosis has also been described as complicating tuberculosis, Hodgkins disease, and sarcoidosis, particularly the latter, if the patient had been on adrenocortical steroid therapy.

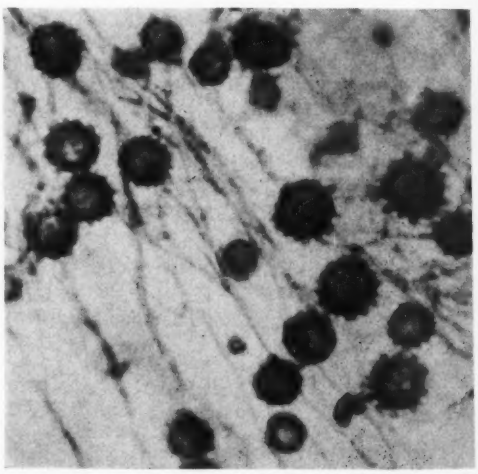
Pathology and mycology. Histoplasma capsulatum is a biphasic fungus which, in tissue and on culture media kept at 37° C., appears as a small yeast (parasitic phase), and at room temperature as a mold (mycelial or saprophytic phase). For diagnostic purposes it takes 2 to 3 weeks for the tuberculate chlamydosphore to develop which is pathognomonic for *H. capsulatum*, and resembles in appearance, the medieval mace.

Histoplasmosis begins with the inhalation of the fungus into the lungs and its deposition in the alveoli, usually adjacent to the pleural or lobar surfaces. A focal granulomatous process begins and the organism usually is engulfed by the reticuloendothelial macrophages. Coagulation necrosis occurs centrally and lymphocytes gather around the lesion. The hilar lymph nodes usually become invaded, particularly in children. In the presence of coagulation necrosis, the yield of identification of the fungus on smear, utilizing the Grocott stain or the periodic acid-Schiff and Gridley stains, is considerably greater than when epithelioid tubercles without necrosis are present.

In the disseminated form, lesions are also found in the adrenals, liver, beyond the regional lymph nodes, spleen, kidney, ileum, buccal cavity, meninges, and bone. Usually the disseminated lesions are ulcerative in character.

Diagnostic procedures. In the geographic areas, particularly in the Southern and Middle Western States, where histoplasmin sensi-

FIG. 5



Photomicrographic enlargement of mycelial phase culture of *Histoplasma capsulatum* obtained from biopsied scalene lymph node (Fig. 4) showing characteristic tuberculate chlamydosphore, resembling a medieval mace in appearance. X 430.

tivity is high, all varieties of histoplasma infections are becoming more frequently recognized. Awareness of the possibility of this disease, enables the clinician to recognize the early phase of the illness and thus utilize more effectively laboratory diagnostic procedures. These include skin tests, serologic determinations of specific antibodies, methods of isolation of fungi, and study of biopsy material on microscopy and culture.

Histoplasmin skin-test sensitivity usually develops about the third or fourth week after the onset of the infection and may remain positive or persist several years after recovery from this infection. It may be the only evidence of previous exposure to this fungus, similar to the positive tuberculin test in relation to tuberculosis. Conversion of a negative reaction with histoplasmin to a positive one is good evidence that the etiologic agent is *H. capsulatum*. It should be noted that a small number of persons who react strongly to this antigen have also, but to a lesser degree, reacted to blastomycin and coccidiodin antigens. Occasionally, in fatal disseminated histoplasmosis the skin test may be negative in the late stage of the disease. Apparently the antigen does not provoke cross reactions to old tuberculin or purified protein derivative (PPD).[17] Our patient reacted strongly to the standard histoplasmin skin antigen, but not to PPD No. 2.

The serologic tests for histoplasmosis may assume considerable importance in recognizing the presence of this disease, particularly in cases of acute pulmonary histoplasmosis, where the organism is difficult to isolate as exemplified in this case. The serologic tests were negative 5 weeks after the onset of clinical symptoms, but the complement fixation test and the hemagglutination test then became positive but were of low titer indicating that the tissue invasion was probably not extensive. Usually antibodies may be demonstrated in the blood during the third or fourth week of the infection, but in this case took between 6 and 7 weeks. The changing titer is considered to be significant (Table 1). It is the policy of our hospital to do weekly serologic tests for histoplasmosis during the first month and then at monthly intervals in order not to miss this change in titer.

The study of biopsy material may be resorted to when the findings in the sputum, gastric contents, urine, blood, and bone marrow aspirate are negative and fail to reveal the organism on smear, culture, or mouse inoculation. This is applicable to this case report. An *impalpable scalene node* was biopsied revealing sarcoid-like nodular collections of epithelioid cells on microscopy. No fungal organisms were found in the aforementioned special fungal stains. However, *H. capsulatum* was cultured from the specimen. Scalene node biopsy has been reported also as an additional aid in diagnosis.

Treatment. Fortunately the great majority of patients with this disease recover. Loewen[18] has followed for several years a number of cases of active pulmonary histoplasmosis with cavitation, as we have, with clinical improvement on hospital bedrest therapy. This was the treatment carried out on the patient in case reported. However, the disease occasionally is characterized by exacerbations and remissions, with exacerbations precipitated by physical activity. When this patient became acutely ill again after a Thanksgiving pass, during which time he exerted himself, he became febrile, and showed increased disease on x-ray examination (Fig. 2). This was followed by remission when he was placed on bedrest in this hospital.

Aside from bedrest, a wide variety of chemotherapeutic or antibiotic agents have been employed in the treatment of histoplasmosis with variable results, among which is included Mycostatin (Squibb), Ethyl Vanillate (Squibb), MRD-112 (Merrell), 2-hydroxystilbamidine (Merrell), and Amphotericin-B (Squibb). Although the sulfonamides have little *in vitro* effect, Christie[19] suggests they may have a place in the treatment of this disease.

Cases of histoplasmosis suitable for evaluation with therapeutic agents include those with,—(a) skin or mucous membrane lesions, (b) chronic active histoplasmosis with cavitation, or (c) cultural evidence of disseminated illness.[15] At the present time we are using Amphotericin-B, which is an antifungal antibiotic derived from a soil streptomycete and which is apparently of value only if given intravenously. Its use is accompanied by some side-reactions, and it is available for hospital use only at the present time. Adrenocortical steroids possibly may prove to be of value in relieving symptoms, and should be used only

when accompanied by treatment with an antifungal agent. Surgical therapy also has been described.[15]

Fortunately, the majority of the patients recover without specific treatment and, as pointed out by Furcolow,[20] "in the great majority of cases of histoplasmosis, the disease probably is of the asymptomatic type."

Summary

This case report illustrates acute pulmonary histoplasmosis, a disease which can be a problem in recognition, diagnosis, and management. The discussion includes differential diagnosis, various diagnostic procedures, and the management of this infectious disease.

Acknowledgment

Appreciation is expressed to Dr. Wheelen D. Sutliff, Chief of Infectious Disease Section, Dr. Sara C. McDearman, Chief of Serologic Section, Miss Elizabeth Ulrich, R.T., Dr. Joseph M. Young, Chief of Laboratory Service, and the Medical Illustration Laboratory of our hospital; to Dr. Michael L. Furcolow, Director, Kansas City Field Station, University of Kansas Medical Center, Kansas City, Kan.; to Dr. Charles E. Andres, Chief of Medical Service, Veterans Administration Hospital, Kansas City, Mo.; and to Dr. William B. Tucker, Chief, Veterans Administration Tuberculosis Unit, Central Office, Washington, D. C., for their assistance or suggestions.

References

1. Lehan, P. H., and Furcolow, M. L.: Epidemic Histoplasmosis, J. Chron. Dis. 5:489, 1957.
2. Darling, S. T.: A Protozoan General Infection Producing Pseudotubercules in the Lung and Focal Necrosis in Liver, Spleen, and Lymph Nodes, J.A.M.A. 46:1283, 1906.
3. Dodd, K., and Tompkins, E. H.: Case of Histoplasmosis of Darling in Infant, Am. J. Trop. Med. 14:127, 1934.
4. DeMonbreun, W. A.: The Cultivation and Cultural Characteristics of Darling's *Histoplasma capsulatum*, Am. J. Trop. Med. 14:93, 1934.
5. Watson, C. J., and Riley, W. A.: A Case of Histoplasmosis Originating in Minnesota, Arch. Path. 1:667, 1926.
6. Hodgson, C. H., Weed, L. A., and Clagett, O. T.: Pulmonary Histoplasmosis: Review of Published Cases and Report of an Unusual Case, J. Thoracic Surg. 20:97, 1950.
7. Long, E. R., and Stearns, W. H.: Physical Examination at Induction. Standards with Respect to Tuberculosis and their Applications as Illustrated by Review of 53,400 X-ray films of Men in the Army of the United States, Radiology 41:144, 1943.
8. Christie, A., and Peterson, J. C.: Pulmonary Calcification in Negative Reactors to Tuberculin, Am. J. Pub. Health 35:1131, 1945.
9. Palmer, C. E.: Non-tuberculous Pulmonary Calcification and Sensitivity to Histoplasmin, Pub. Health Rep. 60:513, 1945.
10. Furcolow, M. L.: Further Observations on Histoplasmosis. Mycology and Bacteriology, Pub. Health Rep. 65:965, 1950.
11. Wilcox, K. R., Waisbren, B. A., and Martin, J.: The Walworth, Wisconsin Epidemic of Histoplasmosis, Ann. Int. Med. 49:388, 1958.
12. Mochi, A., and Edwards, P. Q.: Geographical Distribution of Histoplasmosis and Histoplasmin Sensitivity, Bull. World Health Organ. 5:259, 1952.
13. Emmons, C. W.: Isolation of *Histoplasma capsulatum* from Soil, Pub. Health Rep. 64:892, 1949.
14. Serologic Survey for Histoplasmosis Individual Case Report Form, VA Form 10-2898, June 1957, Veterans Administration—Armed Forces Cooperative Study.
15. Loosli, C. G.: Histoplasmosis, J. Chron. Dis. 5:473, 1957.
16. Sutliff, W. D., and Burkett, L. L.: Chronic Pulmonary Histoplasmosis, Postgrad. Med. 20:125, 1956.
17. Furcolow, M. L.: The Histoplasmin Skin Test, Am. J. Clin. Path. 18:171, 1948.
18. Loewen, D. F., Procknow, J. J., Loosli, C. G., and Tanzi, F.: Chronic Active Pulmonary Histoplasmosis with Cavitation: A Clinical and Laboratory Study, Abstract, Tr. Nat. Tuberc. A. 51st Annual Meeting, 1955.
19. Christie, A.: The Disease Spectrum of Human Histoplasmosis, Ann. Int. Med. 49:544, 1958.
20. Furcolow, M. L.: Clinical Diagnosis of Histoplasmosis, Postgrad. Med. 20:349, 1956.

Discussion (Abstract)

Dr. Fred E. Tosh, Kansas City, Kan. This case illustrates the features common to the more severe nonfatal infections with *Histoplasma capsulatum*. Most infections with this organism are of a much less severe nature and the host overcomes the infection with few if any clinical symptoms. However, in the more severe forms there often develops a balance between the defense mechanisms of the host and the invasive powers of the disease producing organism and minute factors can sway the advantage to either side. In the case presented bedrest alone gave the advantage to the host and improvement was noted; however, overexertion by the patient caused progression of his disease. In cases of this severity it would be desirable to consider specific therapy to shorten the course of the disease and make the patient ambulatory.

Unless histoplasmosis is considered in all influenza-like illnesses, especially those with pulmonary involvement, many cases will be missed and very often confused with atypical or viral pneumonia. Even though the clinical picture and x-ray findings of this infection are often quite similar to those of a number of respiratory diseases, the differentiation can usually be made if one considers histoplasmosis and makes use of the available diagnostic aids. Recently the recognition of histoplasmosis has assumed importance greater than mere academic interest, for one of the newer antibiotics shows promise as an effective agent for the treatment of this disease.[1]

The skin and serologic tests are probably the most important aids in the diagnosis of histoplasmosis. A positive skin test, as in this case, can be interpreted only as indicating past or present infection, but a conversion of the skin test is considered strong evidence of recent infection with *H. capsulatum*.

Serologic tests are invaluable in the diagnosis of histoplasmosis. These tests are positive only during the acute stages of the disease, and the titers tend to fall when healing of the lesions occurs. In acute cases it is desirable to secure both an acute and convalescent serum. Dr. Horton has pointed out that his patient had negative serologic tests on admission to the hospital, but when checked approximately two weeks later the tests had become positive. The serologic tests usually become positive 4 to 6 weeks following infection and remain elevated for about a year, but may be elevated for as long as 5 to 7 years in cases in which severe pulmonary damage has occurred. Serologic tests also appear useful in prognosis inasmuch as a continuing high titer or rising titer later

1. Lehan, P. H., Yates, J. L., Brasher, C. A., Larsh, H. W., and Furcolow, M. L.: Experiences with the Therapy of Sixty Cases of Deep Mycotic Infections, Dis. Chest 32:597, 1957.

in the disease indicates dissemination, and therefore a poor prognosis.[2]

Any patient suspected of having histoplasmosis, especially one with positive serologic tests, should have repeated fungus cultures for isolation of the organism. Culture of the organism is relatively simple provided the laboratory personnel have some basic knowledge of mycology. Otherwise, false negative reports are frequent.

This case certainly illustrates the value of biopsies, where feasible, in making a definitive diagnosis. Any biopsy material removed in cases of questionable etiology should be cultured and stained for fungi. Visualization of the organism is relatively easy if the newer fungus stains are used.

As stated previously, the matter of treatment is extremely pertinent now, since promising results have been obtained using a new antibiotic. This antibiotic, Amphotericin-B (Squibb) has been shown to be an extremely good fungicidal agent and good results have been obtained in a number of fungus infections including histoplasmosis and cryptococcosis. Employment of this antibiotic is not simple inasmuch as it must be given intravenously over a long period of time and pyretic responses often occur during administration. For this reason it has been our policy to use it only in the more severe cases.

Although considerable information about histoplasmosis has been accumulated since it was first described in 1906, it is obvious that much remains to be learned before we will be able to solve the many problems in controlling the disease.

It has been a pleasure to discuss this excellent paper of Dr. Horton's, and I believe we all agree that this subject should receive more attention from the medical profession.

2. Furcolow, M. L.: The Clinical Diagnosis of Histoplasmosis, Postgrad. Med. 20:349, 1956.

HOTEL RESERVATION APPLICATION FORM

FOR 53rd ANNUAL SESSION

ATLANTA, GA., NOVEMBER 16-19, 1959

APPEARS IN THIS ISSUE

MAKE YOUR RESERVATION NOW!

Intussusception in Child and Adult—A Comparison*

GEORGE B. SANDERS, M.D., and DAVID W. KINNAIRD, M.D.,†
Louisville, Ky.

The incidence of intussusception is probably more common than statistics would indicate. The primary lesion to which the intussusception usually is secondary is the one commonly catalogued. Treatment perforce is usually resection in contrast to the preferable treatment in infants.

INTUSSUSCEPTION is the telescoping of a portion of intestine or colon into an adjacent segment of the gastrointestinal tube. It has been known to occur at all points along the gastrointestinal tract from the stomach to the anus. The part of the gut that invaginates is called the intussusceptum; that which receives the invagination is called the intussuscipiens. Usually, an intussusception proceeds distally. Retrograde intussusceptions are, however, occasionally seen in relation to gastrojejunostomy stomas, and as the result of the use of long balloon-tipped intestinal tubes.[1,2]

Intussusception is primarily a disease of infants and children. It is the most common cause of intestinal obstruction in childhood and is second only to appendicitis as a cause of acute abdominal emergency after the first month of life. Though less common in adults, it does occur with significant frequency. Probably less than 10% of cases of intussusception occur in adults, and some studies report the incidence as low as 3 per cent. The available literature on intussusception in children is voluminous, and excellent reviews of fairly large series are available. References to intussusception in adults are more sparse. In a previous report on this subject,[3] we collected approximately 1,252 cases of acute intussusception in adults, as reported in the English and American literature from 1892 to 1957. We propose to report an additional case in an adult of intussusception involving the colon and associated with malignancy bringing our own total of such cases to five and the total number of cases in adults in the English and American literature to 1,253 (Table 1).

TABLE 1

ADULT INTUSSUSCEPTION STATISTICS

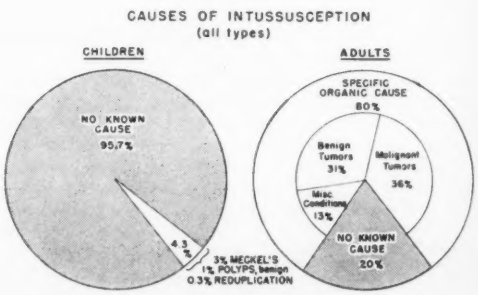
Total cases *adult intussusception* reported in English and American literature since 1892	1,253
Number of cases arising in colon	351
Number of cases due to malignant tumors of colon	240
Number of cases due to, or associated with carcinoma of colon	219

Age and Sex Incidence

As has been previously reported,[4] 80% of intussusceptions in children occur under 2 years of age. Intussusception is infrequent in the newborn, but from the third month on, the incidence rises. Sixty-nine per cent of cases occur during the first year of life and an additional 11% during the second year.

In adults, considering all types of intussusception, it is found that two-thirds of the cases reported occurred before the age of forty-five. In both adults and children the condition occurs twice as often in males as in females.[5]

FIG. 1



*Read before the Section on Surgery, Southern Medical Association, Fifty-Second Annual Meeting, New Orleans, La., November 3-6, 1958.

†From the Department of Surgery, University of Louisville School of Medicine and the Surgical Service, Norton Memorial Infirmary, Louisville, Ky.

Etiology

In 95% of cases in children, no specific cause for the intussusception will be found. In adults, by contrast, 80% are due to some specific organic lesion. In the small percentage of children in whom some organic lesion is present, in 3%, this proves to be a Meckel's diverticulum, in 1%, a benign polyp, and in 0.3%, reduplication of the bowel[4] (Fig. 1).

In adults with a known organic cause for intussusception, the most recent reports reveal a striking association of this lesion with malignancy,[6] especially when intussusceptions of the colon are considered. It has been found that 62.2% of intussusceptions in adults involving the large bowel are caused by, or are associated with, a carcinoma.[4] In children, on the contrary, malignancy as the cause of intussusception is virtually unknown (Fig. 2).

Types of Intussusception

Intussusceptions are best classified by naming first the intussusceptum or the invaginating portion of the bowel followed by the intussuscipiens or receiving portion of the bowel. The several possible varieties of intussusception confined to the small intestine are grouped under the term enteric. The corresponding term for intussusception of one portion of the colon into another is colocolic. Several possibilities are present in the region of the ileocecal valve. These are: the ileocolic, in which the ileum is the leading point into the colon; and the ileocecal, in which the cecum is the leading point bringing the ileum along with it (Fig. 3). Clinically, these are often indistinguishable. Double intussusception may occur, such as the ileo-ileocolic. This begins as an ileo-ileac intussusception, the entire mass then invaginating into the colon. It is also possible to have more than one area of the intestinal tract involved in intussusception at the same time.

FIG. 2

ADULT INTUSSUSCEPTION AND MALIGNANCY

Colonic Only

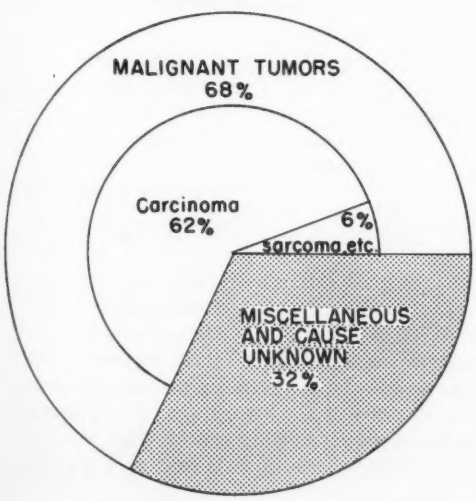
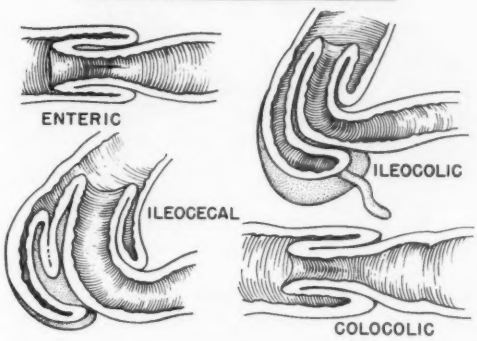


FIG. 3

TYPES OF INTUSSUSCEPTION



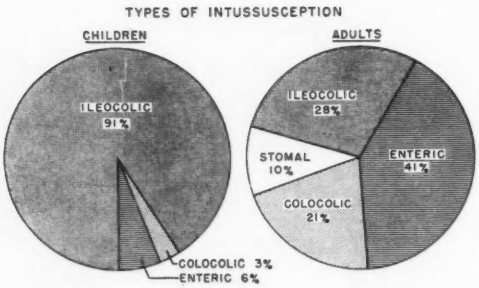
One of the most unusual cases recorded was that reported by Coleman[7] in 1941. This patient had an intussusception of the jejunum, which at one point showed nine layers, that is, the intussusception was compounded four times.

The most common type of intussusception in children is the ileocolic, accounting for 91% of cases. Of the remainder, 6% are enteric, and 3% colocolic. In adults, intussusception more commonly involves the small bowel only; the enteric variety represents 41% of the total, ileocolic 28%, and colocolic 21 per cent[5] (Fig. 4).

Symptomatology and Diagnosis

The symptoms and rapidly progressive course of acute intussusception in children is so characteristic and well known that the customarily well-fed appearance of the patient and the intervals free of pain should deceive only the inexperienced. The symptom triad

FIG. 4



of intermittent abdominal pain, vomiting, and bloody rectal passages are diagnostic. Occasionally the latter has to be sought for by digital examination of the rectum.

In adults, the clinical manifestations are so atypical that a characteristic syndrome cannot be described. If anything, chronicity and recurrence of obstructive symptoms characterizes the adult form. The specific organic cause of the intussusception, present in 8 out of 10 adult cases, may produce misleading symptoms. Almost all adult patients with intussusception have recurring attacks, varying in severity, of cramping abdominal pain, nausea, and vomiting over an extended period. Diagnosis often eludes the physician until a severe, acute episode leads to laparotomy. Because of the prevalence of the enteric type of intussusception in adults, bloody rectal passage is less frequent, delayed and often absent. When present, it is usually from ulceration of an underlying tumor.

In children the cardinal physical finding is a palpable mass, described as sausage or banana shaped. In combination with the triad of symptoms already described, it makes diagnosis obvious.

In adults the more developed abdominal musculature makes deep palpation less revealing. Then too, the prevalence of the enteric type, which is the hardest to palpate, adds to the difficulties in the adult. Moreover, finding a mass in an adult abdomen suggests other more common conditions than intussusception.

The one phase of examination that is almost equally rewarding in both child and adult is the examination of the colon by barium enema. Most childhood intussusceptions can be diagnosed without its aid, but such studies are recommended if doubt exists. In the adult the frequently bizarre and nonspecific clinical picture of intussusception can often be resolved only by diagnostic barium enema.

The x-ray findings in children and adults are similar, and have been described by Orloff:

"1. There is obstruction to the flow of barium and if the intussusception is reducible this obstruction recedes as the pressure is increased.

"2. As the barium meets the head of the intussusception, a cupola, or crescent-shaped figure, is seen at the end of the column.

"3. If barium is able to pass between the sheaths of the invagination, the cupola changes to a fork, pincers or U-shaped figure.

"4. As the barium passes further between the sheaths and fills the narrow spaces, a series of rings of 'coiled-spring' configuration appears. This is best observed on postevacuation films.

"5. If the barium is able to pass around the intussusceptum completely, it is seen as a shell surrounding a rounded central filling defect.

"6. A mass is palpable at the initial point of obstruction to barium flow.

"7. Often, gaseous dilatation of the terminal ileum just proximal to the intussusception is seen. Occasionally barium enters the lumen of the intussusceptum and appears as a streak parallel to the long axis of the bowel."[4]

However, if the intussusception is enteric, the most common form in adults, the barium enema will not reveal it, and it has been recommended that a barium meal be given. This would hardly seem necessary and actually might be dangerous in children, but in the adult with a bowel prepared for operation, the hazard is much less and the information vital.

The characteristic x-ray findings of examination by barium meal in enteric intussusceptions are:

"1. Delayed emptying time

"2. A beak-shaped stricture

"3. A series of concentric rings from barium reflux between the sheaths of the intussusception.

"4. Dilatation of the intestine just proximal to the stricture."[4]

Certain differences of diagnostic and prognostic importance between malignant and benign intussusceptions in adults have been well pointed out by Roper.[6] In his series, the average age of the patients in the benign group was 40 years. The average age of the patients in the malignant group was 53 years. A malignant etiology should, therefore, as Roper sug-

gests, be suspected in the patient over 50, but it is well to remember that the occasional adolescent or young adult will have a malignancy, often of an anaplastic type. Roper found striking differences in the total duration of the condition and of symptoms when the two groups were compared. In the group of benign tumors, the average duration of symptoms was 15 months, and the majority of patients gave a story of recurring abdominal crises of varying frequency and severity, culminating in the final obstruction for which operation was required. In between the attacks of abdominal pain the patients were well, though about half of them lost weight. In the group with malignant lesions the average duration of symptoms was only 10 weeks. Between attacks the patients were reasonably well, but in the malignant group either the patient or his relatives had noted deterioration in the 3 or 4 months prior to the final instance. In both groups, unlike the infantile type of intussusception, only one-third of the patients gave a history of rectal bleeding or were found to have blood in the stools.

Treatment

The treatment accorded an intussusception can be categorized as follows: (1) nonoperative; (2) operative, either by (a) reduction, or by (b) resection.

Nonoperative. Recently there has been a revival of interest in the treatment of intussusceptions by reduction by barium enema. Opinions differ as to the advisability of employing this method either as a definitive treatment or as a preliminary effort in early acute intussusception in children. There is much to be said for the method especially if the routine precautions, as outlined by Orloff and others,[3,8,9] are rigidly followed. There are also valid objections to its use based on:

1. The uncertainty, at times, that the intussusception has been completely reduced.

2. An ileac portion of an intussusception may be left unreduced.

3. An existing ileac polyp or Meckel's diverticulum, an occasional cause of childhood intussusception, will be completely overlooked.[4]

4. A segment of gangrenous or perforated intestine may be unwittingly reduced.

The method should *never* be used in the adult form because:

1. The majority of intussusceptions are enteric.

2. The majority of intussusceptions have an organic basis requiring surgical attention.

3. The frequent association with malignant tumors makes operation mandatory.[3]

Operative reduction. By operative reduction is meant the manual reduction of the intussusception at, or during laparotomy by the maneuver of taxis. Undoubtedly the cardinal form of treatment in infants, its success depends largely on early diagnosis and prompt operation, both arguments against the loss of time entailed by attempts at nonoperative treatment. A direct correlation exists between the shortness of the duration of symptoms, the ease of reduction, and the mortality, in intussusception in infants.

While ideal in infants and young children, it is not so satisfactory in adults because the chronicity of intussusception in adults greatly lowers the percentage of reducible cases. Similarly, the organic basis for 8 out of 10 adult intussusceptions usually makes some form of resection a probability while the association with malignancy in 4 out of 10 cases makes resection necessary. In colonic intussusceptions, especially, the causative carcinoma not only requires resection but, as we shall see, makes reduction extremely inadvisable.

Resection. In infants, where delay or other causes have rendered an intussusception irreducible or where, once reduced, the intestine has been sufficiently damaged, or when a child is critically ill, it becomes necessary at times to resect either the unreduced intussusception or the damaged intestine. Even though resection can now be accomplished with a much lower mortality than heretofore, this surgical extremity is always rightly dreaded in infants for the mortality is still high. The decision to complete the resection by either primary anastomosis or a Mikulicz procedure will rest upon the patient's condition and the skill and experience of the surgeon. Certainly it has been shown that a resection and primary anastomosis can be done under these conditions with an acceptable mortality.[9,10]

In adults, by and large, resection of the unreduced or partly reduced intussusception is the treatment of choice. The organic basis and

association with malignancy of a sizable group of adult intussusceptions has already been commented upon. In the case of colonic intussusceptions especially, where 68% are caused by a malignant tumor, it is vital that no effort at operative reduction of an adult intussusception be attempted.

Unlike the child, the adult withstands extensive colonic resections well, even in the face of obstruction. With the advent of effective antibiotics and with increased knowledge of surgical physiology, improved technics of bowel anastomosis, vastly improved anesthesia and postoperative management, resection, even for possibly benign lesions, is the treatment of choice in adult colonic intussusceptions. The extent of resection should be such that not only the intussusception but also the associated malignancy if present is removed completely and safely by an adequate cancer operation.

Consequently, for lesions of the right half of the colon and transverse colon to the splenic flexure, a right hemicolectomy, or right three-quarter colectomy, might well be necessary, with end-to-end anastomosis of terminal ileum to distal colon if, in the best judgment of the surgeon, primary anastomosis can safely be done. For lesions of the splenic flexure and descending colon down to the lower sigmoid, resection of the left half of the transverse colon, descending and sigmoid colon may be done with anastomosis, if feasible, of proximal transverse colon to rectosigmoid. Lesions of the low sigmoid or rectosigmoid should probably have a Miles combined abdominoperineal resection, although in some cases it may be permissible, in this situation only, to attempt reduction at the operating table so an anterior resection may be done for a low-lying, rectosigmoid lesion, sparing a debilitated patient the rigors of the more radical operation.

Whether primary anastomosis, with or without proximal decompression, should follow resection of the intussusception depends on the judgment and skill of the surgeon, the duration and completeness of the obstruction, the condition of patient and bowel, and the general situation in the abdomen as revealed by laparotomy. In certain instances of longstanding obstruction with an unprepared bowel, nothing more than proximal cecostomy or colostomy as a first stage procedure would indicate good judgment. It is of interest that an irreducible intussusception of this type will usually become reducible, or may reduce spontaneously following such a procedure. After adequate decompression, accurate location of the malignant lesion by barium studies, and adequate preparation of the bowel with antibiotics, a definitive resection of wide scope for cancer may then be done with comparative safety. In some low-lying sigmoidorectal intussusceptions, such a staged operation may occasionally permit the performance of a low anterior resection as a definitive curative operation.[3]

Intussuscepting Carcinoma of the Colon

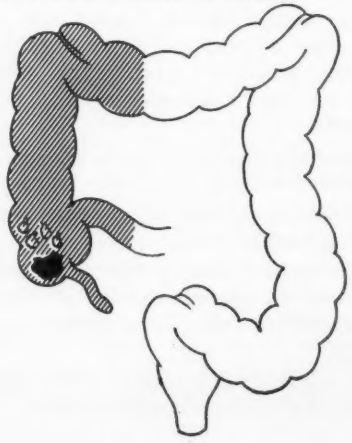
This somewhat unusual condition, which occurs with significant frequency, however, (Table 1) has attracted our interest and prompted a previous study[3] in which we reported 4 cases. Since then we have encountered another such case in which we were enabled by previous studies and conclusions to treat in a surgically optimal manner.

Case Report. A 71 year old white woman was ad-

FIG. 5

CASE V

1. 71 year old white female.
2. 4 months history of intermittent obstruction, rectal bleeding.
3. Barium enema showed polypoid mass in cecum.
4. Intussusception palpable, right iliac fossa.
5. Right hemicolectomy and primary anastomosis.
6. CA cecum – nodes negative.



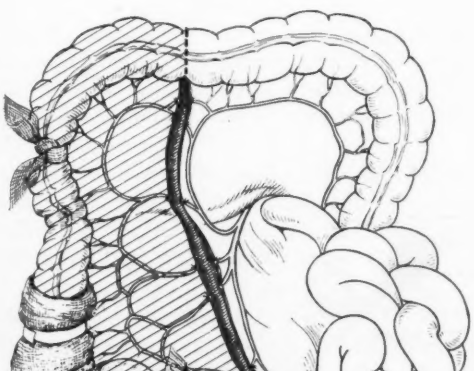
mitted to the hospital with a history of recurring attacks of central abdominal pain, nausea, and abdominal distention. In 4 months time, she had suffered 8 to 10 attacks. During the last attack, which subsided spontaneously 5 days before admission, some cherry-red and purplish blood was observed in the stools. This had not been noted previously.

Physical examination did not reveal a mass at first, possibly because of abdominal distention, but 48 hours later, a moderately tender, large, banana-shaped, firm mass was easily palpable in the right iliac fossa. Twenty-four hours later the mass, although still palpable, was much smaller and was located lower and deeper in the iliac fossa. Barium enema showed a large, nonobstructing, polypoid mass in the head of the cecum.

A tentative diagnosis of intussuscepting polypoid carcinoma of the cecum was made (Fig. 5).

After preliminary preparation of the colon with antibiotics, the patient was operated on and, as the abdomen was opened, an intussusception involving the cecum, ileocecal junction and cecocolic junction was seen. No attempt at investigation or reduction of the intussusception was made, but preparations were made at once to do a resection in accordance with the principles of adequate cancer surgery as follows: The intussusception was partly wrapped with a dry laparotomy sponge. Preliminary mobilization of the cecum along the lateral gutter permitted complete protective envelopment of the intussusception mass by the laparotomy pad which was then tied in place with two strips of umbilical tape. Next, the vascular supply of the right hemicolon was interrupted by ligation and division of the right branches of the middle colic vessels, the right colic vessels and the ileocolic vessels. Next the bowel was occluded proximal and distal to the carcinoma-bearing intussusception by gauze tapes tied tightly around the ascending colon and terminal ileum (Fig. 6). Finally, the right hemicolon from the midportion of the transcolon to the terminal 6 inches of ileum along with a wide portion of lateral peritoneal attachments and the entire right mesocolon and regional lymph nodes was resected. The operation was completed by an end-to-end anastomosis using one layer of nonabsorbable mattress sutures of fine cotton.

FIG. 6



CASE V: PLANNED RIGHT HEMICOLECTOMY FOR INTUSSUSCEPTING CARCINOMA OF CECUM.

The postoperative course was uneventful. The patient was passing flatus and stool per rectum in 36 hours.

The pathologist reported a gelatinous, polypoid adenocarcinoma of the cecum with negative regional nodes.

Summary

Intussusception, primarily a disease of infants and children, occurs in adults not infrequently. Significant differences are found between childhood and adult forms in regard to etiology, sex incidence, and location, which profoundly affect the ease of diagnosis, the form of treatment, and finally the prognosis. The association with malignancy is rare in the childhood form in which the mortality is directly related to the ease of reduction or the magnitude of the surgical procedure necessary to relieve or remove the intussusception itself. In the adult, the mortality reflects the natural history of the underlying organic cause or lesion, often a malignancy.

Because of the high association with malignancy, adult intussusceptions, especially those of the colon, are preferably treated by radical resection according to the tenets of adequate cancer surgery. Conservative surgical measures applicable, and indeed preferable, in children are unwise in the adult. The American and English literature on intussusception in adults has been reviewed since 1892, and a case of intussuscepting carcinoma of the colon has been added to our previous group of 4 cases reported in an earlier paper.

References

1. McGoon, D. C.: Intussusception, A Hazard of Intestinal Intubation, Surgery 40:515, 1946.
2. ReMine, W. H., and Pontius, John G.: Intussusception of the Small Bowel as a Complication of the Use of a Long Limbed Intestinal Tube, Proc. Staff Meet. Mayo Clin. 33:451, 1958.
3. Sanders, George B., and Hagan, William H.: Adult Intussusception and Carcinoma of the Colon, Ann. Surg. 147:796, 1958.
4. Orloff, M. J.: Intussusception in Children and Adults, Internat. Abstr. Surg. 102:313, 1956.
5. Donhauser, J. L., and Kelly, E. C.: Intussusception in the Adult, Am. J. Surg. 79:673, 1950.
6. Roper, A.: Intussusception in Adults, Surg. Gynec. & Obst. 103:267, 1956.
7. Coleman, E. P., McGuire, R. H., and Bennett, D. A.: Recurring Jejunal Intussusception, Am. J. Surg. 53:340, 1941.
8. Ravitch, M. M.: Reduction of Intussusception by Barium Enema, Surg. Gynec. & Obst. 99:431, 1954.
9. Packard, G. B., and Allen, R. P.: Results in the Treatment of Intussusception in Infants and Children, Surgery 41:567, 1957.

10. Dennis, C.: Resection and Primary Anastomosis in the Treatment of Gangrenous or Non-reducible Intussusception in Children, Ann. Surg. 126:788, 1947.

Discussion (Abstract)

Dr. Bernard J. Schoo, Louisville, Ky. This is certainly an excellent paper presented in a very interesting manner. It is particularly significant since so little has been written about intussusception in adults. I do not believe it is as rare as the literature indicates. Only recently I reviewed all cases of intussusception in children over a 5 year period in all the hospitals in Louisville, Kentucky, and incidentally found 10 cases of intussusception in adults as compared to 62 cases in children. Frequently, these cases are not coded in record rooms because the physician signs the chart according to the tumor or other disease causing the intussusception.

The authors state that 68% of all colonic intussusceptions are due to malignancy. This high percentage, coupled with the many recent reports of viable cancer cells floating freely in the blood stream, emphasizes their conclusion that no attempt should be made to reduce a colonic intussusception. A primary resection represents very sound judgment. However, I would like to ask Dr. Sanders how he definitely establishes the diagnosis of malignancy in these edematous intussusceptions before he embarks upon a cancer operation.

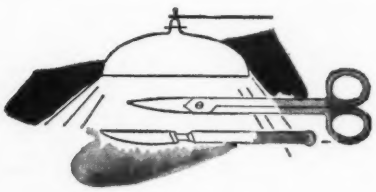
Dr. Sanders knows that my primary interest lies in caring for children, and I would like to emphasize his paper by contrasting his statistics and conclusions with a very practical series of intussusceptions in infants with which I have dealt.

The *first slide* represents a compilation of all cases of intussusception in children in the city of Louisville. This series demonstrates that many of the older children with intussusception are treated in hospitals for adults. Only 51% of this series were under 2 years of age. However, if one inspects the statistics from our Children's Hospital, they correspond very closely to the usual statements that 75 to 80% of all intussusceptions occur under 2 years of age. Even though intussusception is more common in infancy, it should not be forgotten if the symptoms are present in an older child.

The *second slide* demonstrates that few of these percentages correspond with what is found in the usual intussusception in adults. As the authors have pointed out, a palpable mass is rarely present. A definite etiology is present in about 80% of adults. There is no seasonal incidence, and the adult patient very commonly shows early signs of deterioration.

The *third slide* compares our relatively conservative therapy versus immediate primary resection of the bowel as advocated by the authors for adult colonic intussusception. It should be mentioned that the most common intussusception in adults and children is the ileal and ileocolonic type. None of these cases were of the colonic type and all cases were diagnosed correctly before operation. This is quite a contrast to the authors' findings in the adult, where the diagnosis is rarely made before operation and where the colonic type makes up 25% of the cases. I wish to thank Dr. Sanders for this opportunity to comment on his paper and for making these comparisons.

Dr. Sanders (Closing). I wish to thank Dr. Schoo for his fine discussion. In answer to his question as to how one could definitely establish the diagnosis of malignancy in intussusception in an adult before proceeding with an extensive resection, I must say that it is impossible and impractical as well as, I think, unwise to attempt to do so. The only way would be to biopsy the lesion after reducing the intussusception, and this is what one must not do for fear of spreading the malignancy which is frequently present. I think that one must accept the fact that over 60% of intussusceptions of the colon in adults, at any rate, will be associated with a malignancy and that, therefore, a very wide resection is the treatment of choice. Even if one finds afterward that such a resection has been done for a benign lesion, the harm is minimal and certainly not to be compared with the damage done by meddling with a malignant intussusception.



Anticholinergic Anesthesia*

CLARENCE W. LEGERTON, JR., M.D., *Charleston, S. C.*

The anticholinergic drugs given orally appear to have little if any effect in the control of the secretion of acid. Rather their effect seems to be that of an anesthetic in the presence of peptic ulcer, merely controlling pain. The danger of their use lies in the suppression of the warning signal of pain upon recurrence of an ulcer or of some of its complications.

WHENEVER A NEW THERAPEUTIC AGENT is introduced in the treatment of peptic ulcer disease, its evaluation seems to go through three phases. The initial phase is one of great optimism, marked by small series of cases and brief follow-up observations. This is soon replaced by the second phase—that of careful evaluation—which is of longer duration and consists of more astute and less partisan observations. Lastly, there comes the stage of limited pessimism, in which it is realized that the drug perhaps has a place in ulcer therapy, but that this place is a limited one, that there are contraindications and perhaps hazards to its use, and that it is definitely not the panacea so eagerly hoped for in the earlier stages of evaluation.

It would seem now that the anticholinergic drugs have about come full circle, and that we are in phase three of their evaluation as specifics in ulcer therapy.

Shortly after these drugs were introduced there was much enthusiasm, and some authorities even stated that these agents were of such value that conventional medical measures were no longer necessary, recurrences could be prevented, and even that the need for surgery could be markedly reduced or obviated.[1]

As a result of this and other glowing reports, hundreds of ulcer patients hastened to use these agents, both during the active and the interim phase of their disease.

Soon phase two was entered, and physicians using these drugs began to see that the initial enthusiasm was unwarranted; more critical investigations failed to confirm some of the original observations. Perhaps the best long-term evaluation of these agents was the one carried out by Ruffin and associates,[2] utilizing the "double-blind" technic. This study pointed up the fact that while the patient with peptic ulcer may have fewer and milder recurrences when maintained on anticholinergic agents than on atropine or a placebo, these agents do not prevent complications and do not either appreciably reduce or obviate the need for surgery. Other authorities have subsequently confirmed his observation that the eventual course of peptic ulcer does not appear to be altered by the administration of these agents.[3-6] It is of interest that the symptomatic improvement noted in Ruffin's series was inversely proportional to the estimated degree of severity of the ulcer. The mild cases did extremely well on the anticholinergic agents while in the severe cases the results were only fair. Perhaps these agents are able to suppress the mechanism responsible for pain in milder cases, but in more severe cases the pain is able to "break through" the pain-relieving effect of orally administered anticholinergic drugs.

In the past year, I believe, we have entered the third phase in our evaluation of these drugs. We no longer use them indiscriminately, and we recognize certain clear-cut contraindications to their use, such as obstruction at the pylorus.

However, we continue to see patients who have been placed on anticholinergic therapy during their acute ulcer distress, and who then continue the use of these drugs during the quiescent phase of their disease, often with the idea that such use is an effective "prophylactic measure." Those who have had an opportunity to follow such patients are beginning to see that not only do these drugs fail to alter the eventual course of ulcer disease, but in some cases their use in long-term ulcer management may actually be harmful.

*Read before the Section on Gastroenterology, Southern Medical Association, Fifty-Second Annual Meeting, New Orleans, La., November 3-6, 1958.

It is the purpose of this paper to document some of the hazards which occur in ulcer patients who are maintained on anticholinergic therapy over prolonged periods of time. The thesis is presented that while these drugs may reduce the frequency or severity of episodes of subjective ulcer distress, their use does not result in the formation of less ulcer craters than would occur if they were not used. Rather they have the effect of relieving the patient of his warning symptom of pain, most probably by depressing the mechanism which produces ulcer pain. Hence we are "anesthetizing" the ulcer rather than healing it, and this "anticholinergic anesthesia" is frequently neither advisable nor wise, and in certain cases may actually lead to harm.

Case Reports

Case 1. O. L., a 58 year old white man, first developed gnawing epigastric pain on an empty stomach, relieved by milk and antacids, in 1939. Recurrences would occur three or four times a year, lasting about 2 weeks. Nocturnal pain was present during periods of ulcer activity. With the onset of typical distress, the patient would seek medical advice, modify his diet, and begin medication. Response to these measures was usually satisfactory, although during one of these episodes in the fall of 1955 he had a perforation of his ulcer (duodenal) which was closed surgically.

Following this he had symptoms almost daily for 5 months. When first seen in Apr., 1956, a G.I. series revealed an active duodenal ulcer with marked deformity of the bulb.

His ulcer distress responded rapidly to a medical ulcer program plus the use of a new anticholinergic, hexocyclium (Abbott). Over the next 8 months he remained relatively symptom-free. However, on two or three nights a month he would be awakened at about 2 o'clock A.M. by mild epigastric distress, immediately relieved by milk. There was no pain during daylight hours.

In Jan., 1957, because of the persistence of these mild symptoms and in spite of cooperation by the patient in diet and medication, a second upper G.I. series was done. This revealed a deep crater in the duodenum, measuring 0.5 cm. in diameter at its base. This was much larger than the one present after 5 months of ulcer distress (and without anticholinergics) at the beginning of his treatment.

Accordingly, he was immediately placed on a rigid Sippy diet, frequent antacids, sedatives and asked to discontinue his work temporarily. On this program all symptoms disappeared and spot films of the duodenal bulb 10 days later showed only a tiny niche at the site of the previous crater. Since then there has been no nocturnal distress.

Comment. In this case the presence of an active ulcer was suspected solely because the patient persisted in having mild nocturnal symptoms in spite of full dosage of anticholinergic drugs and a moderate ulcer diet. With the thought that the day-time symptom of pain might simply have been anesthetized by the effect of hexocyclium, x-ray examinations were made and a rather large active ulcer was found. This in spite of the fact that both physician and patient were well pleased with the response to medication, the patient stating that the preceding 8 months were the "best he had had in years."

It is interesting to speculate as to whether or not the crater would have progressed to a second perforation had x-ray studies not been done and a radical change made in the medical program.

Case 2. J. Z., a 63 year old clerk, had had typical ulcer distress each spring for the preceding 5 years. During 2 of these years he had also had recurrences in the fall. It was of interest that the patient spontaneously stated that he would, "do fine if I could only omit the second week of April," as that was invariably the date of his recurrence. During his fall recurrence in 1956 he was placed on usual ulcer therapy including Prolonged Action Pro-Banthine (30 mg. b.i.d.). He made a prompt response and x-ray studies confirmed healing of the crater. The Prolonged Action Pro-Banthine was continued.

Because of the patient's voluntary statement that the second week of April was the time of his recurrences in previous years, an upper G.I. series was done at that time (Apr. 9, 1957) in spite of a complete lack of ulcer symptoms. Surprisingly the crater of an active ulcer was demonstrated, requiring further restrictions in his regimen. Following the x-ray visualization of the crater, detailed questioning was again carried out, without being able to get the patient to admit even the slightest digestive discomfort.

Comment. Had an x-ray examination not been done out of academic interest, this patient would have been classed as having had an excellent response, with the first symptom-free spring in 5 years. Surely in this case the previous symptoms of pain had been anesthetized. It is interesting to speculate whether this ulcer would have healed spontaneously or would have progressed to hemorrhage or perforation, since, in the absence of pain, the patient would not have modified his diet or sought medical aid.

Case 3. W. H., a 22 year old telegraph operator, first developed ulcer distress in the fall of 1953. Recurrences were manifested by pain, and responded to diet and antacids. In Oct., 1956, following 3 days of ulcer distress for which he did little, as he was away from home working with a railroad crew, he awoke one night with massive hematemesis and melena. Eight transfusions were required. He was then placed on an

anticholinergic agent in the usual dosage as a "prophylactic measure." He did well until Apr. 16, 1957, when he passed a "dark brown" stool and noted mild anorexia. Since he had no epigastric distress he paid little attention to either the symptom or the sign. The following morning he had no appetite for breakfast and again passed a "dark brown" stool. Mild weakness and slight nausea followed, and he returned to bed and began a program of milk hourly. That afternoon, still without pain, he passed two maroon-black stools, realized he was again bleeding and was brought to the hospital.

Comment. Here again the masking of antecedent epigastric distress, usually felt by the patient, lulled him into a false sense of security and caused him to be unaware of his complication and to delay medical attention. Of course bleeding without antecedent distress might have occurred even without the use of anticholinergic drugs, but this patient previously always had typical ulcer distress with his recurrences and prior to his first hemorrhage.

Case 4. J. McC., a 42 year old carpenter, gave a 12 year history of fall and spring recurrences of typical ulcer distress, usually lasting 10 to 14 days, and responding to dietary changes and relatively simple medical measures. Repeated upper G.I. series had shown a badly scarred duodenal bulb, usually with a demonstrable crater, as these were done mainly during recurrences. Films taken in Sept., 1954, revealed no delay in gastric emptying.

Shortly thereafter he was placed on an anticholinergic agent with what he and his physician felt were excellent results. For the next 3 years he had no ulcer pain and missed no time from work. Three and a half years after being placed on this drug, in the spring of 1958, he presented with postprandial distress, a 20 pound weight loss, and recent onset of vomiting of retained gastric contents. Physical examination showed gastric peristaltic waves visible through the abdominal wall and x-ray studies confirmed a high grade (90% in 6 hours) pyloric obstruction. This improved only slightly on discontinuing the anticholinergic drug and a subtotal resection was carried out, revealing extensive cicatrix formation at the gastric outlet from chronic peptic ulceration.

Comment. Here again one would have to say that peptic ulceration had continued at intervals for the three and a half years during which this patient was free of his usual ulcer pain. It would be unlikely for scarring to advance to such a degree over so long a time unless fresh ulcerations and additional scarring had occurred at intervals. Perhaps had the patient not been relieved of his pain, his total medical program would have been at least somewhat better and possibly pyloric obstruction might not have occurred, or at least occurred later and been preceded by some warning of its impending approach.

Case 5. W. D., a 48 year old carpenter, gave a typical ulcer history dating back to 1942. Recurrences were present two or three times a year, almost invariably in the spring of the year and the fall. In 1954, he was placed on propantheline bromide (15 mg. t.i.d. and 30 mg. h.s.). On this therapy he was improved symptomatically, having no recurrence of ulcer (or at least no ulcer pain) until the fall of 1956. About 11 o'clock one morning, while at work, he suddenly experienced severe abdominal pain. Emergency operation was necessary, with suture of a perforated ulcer on the anterior wall of the duodenum.

Comment. Here again ulcer pain was absent while on anticholinergic therapy given "to prevent recurrences." However, the absence of pain does not necessarily mean the absence of ulcer. If pain had occurred, perhaps adequate ulcer-management would have prevented the complication of perforation. Certainly perforation can occur without preceding pain, but in this case one would feel that pain would have been present had it not been "anesthetized" by propantheline.

Discussion

In light of more recent knowledge concerning these cholinergic blocking agents, one wonders whence came the great initial enthusiasm for these drugs in ulcer disease. Surely it was because of the rapid and often dramatic relief of pain which could be obtained by their use, especially when given parenterally.[7,8] And yet we know that the time required for anatomic healing of an ulcer crater is from 4 to 6 weeks. This observation alone should make us aware that relief of pain and healing of an ulcer do not occur simultaneously. Perhaps we have allowed ourselves to fall into the old trap of treating the symptom rather than the disease. In the great majority of cases of uncomplicated peptic ulcer the symptom which leads the patient to seek medical attention is pain. The physician knows that the pain is a result of the ulcer, and is liable to jump to the unjustified conclusion that once the pain is gone, the ulcer is gone also. We must remember that our primary objective is to heal the ulcer, a by-product of which is the relief of the pain produced by that ulcer.

There are two major schools of thought as to the mechanism whereby pain of peptic ulcer is relieved by anticholinergic drugs:

one believes that it is due to depression of the acid level, the other to abolition of abnormal motility and spasm.

Since we know that acid is necessary for the production of an ulcer, and that it is the usual stimulus for the pain of ulcer, we would logically assume that pain is relieved by abolishing acid or by depressing it below the level necessary for the production of pain.

The striking clinical picture of relief of pain almost immediately following the parenteral use of these drugs argues against the thesis that acid has suddenly been abolished or lowered below the threshold necessary for pain. Nor is the relief of pain due to a failure of acid chyme to reach the ulcer site because of a cessation of gastric motility and evacuation, since it has been shown that the relief of pain is synchronous with cessation of gastric motility, despite artificially produced high levels of acid and the fluoroscopic and radiographic evidence of acid-barium in the ulcer crater.[9] These and other studies have shown that the relief of pain in peptic ulcer by these drugs is almost certainly due to the effect they have upon gastroduodenal motility.[7,9-11] It is known that the effect of these drugs on motility is almost invariably more pronounced and less variable than their effect on secretion.[12]

Since relief of pain is apparently achieved by abolishing abnormal motility and spasm, and not by depressing or abolishing acid, and since a sustained reduction in acid levels is necessary for healing, it follows that the cholinergic-blocking agents do not supplant other conventional methods aimed at reduction or eradication of acid and that they, *per se*, do not play a very important part in healing of the crater.

It is true that acid levels can be consistently lowered and maintained at a lower level when these agents are administered parenterally. However, in the average case of ulcer this therapy is not feasible and the drug is given orally, where it has a much less constant effect or even no effect. When an effect is obtained, side-effects are often so distressing that this effective dose cannot be maintained. Kirsner[13] has pointed out that basal acid secretion is not lowered appreciably, and in several studies the effect on acid obtained when these drugs are given orally is comparable to the effect obtained with placebos.[4,5] If this is true in patients under hospital observation, it is even more likely to be true in patients taking these drugs orally in the interim phases of their ulcer disease while engaging in the pressures and stresses of day-to-day living.

It is evident that the oral use of these drugs does not appreciably reduce the tremondous output of acid produced in response to neurogenic, chemical, hormonal and other influences. Sun and Shay[14] found that usual doses were ineffective in suppressing basal gastric secretion in most cases and often added nothing to the milk and cream mixture in suppressing "digestive" secretion. Kirsner and Palmer[15] have said that, "the effective lowering of gastric secretion during oral administration for long periods of time with little or no side-effects and without toxic reactions, has not been obtained." Thus, if acid is not lowered and kept low, but the pain of an ulcer recurrence is masked by the effects of these drugs on motility and spasm, we can well understand both why pain is less frequently noted and why the long-term course of ulcer disease is not improved.

This elimination of pain as a protective warning sign of ulcer recurrence gives the patient and the physician a false sense of security, leading the physician to perhaps relax other important features of ulcer management and leading the patient to feel that perhaps these other rigid restrictions are not really necessary. Thus, the patient does not get the advantage of the early institution of time-proven measures of ulcer management with the first signs of recurrence.

In the same fashion, the absence of pain misleads the patient into feeling his ulcer is healed, yet at that very time the ulcer may be enlarging or penetrating more deeply and recurrence is recognized only when a complication occurs.[6]

Conclusions

1. Present anticholinergic drugs, orally administered, do not significantly depress day-to-day gastric acid secretion.

2. The pain of a mild ulcer recurrence may be "anesthetized" by these drugs through their effect in depressing the mechanism responsible for the production of pain, i.e. disordered gastroduodenal motility.

3. In spite of this symptomatic improvement (noted mainly in milder cases) it is probable that the ulcer crater recurs with the same frequency whether on anticholinergic medication or not.

4. Anticholinergic agents should not be used for the long-term therapy of peptic ulcer disease, or as "prophylactic therapy." Used in such ways these drugs are of no real value and in certain cases may actually be harmful.

5. Less harm will be done if these drugs, at least in the usual doses given orally, are considered merely as superior "ulcer anesthetic agents."

References

1. Grimson, K. S., Lyons, C. K., and Reeves, R. J.: Clinical Trial of Banthine in 100 Patients with Peptic Ulcer, J.A.M.A. 143:873, 1950.
2. Texter, E. C., Legerton, C. W., and Ruffin, J. M.: Prolonged Drug Therapy in Peptic Ulcer, South. M. J. 46:1062, 1953.
3. Cayer, D., Sohmer, M. F., and Sugg, W. C.: The Effect of Prolonged Continuous Therapy on the Course of Chronic, Recurring Peptic Ulcer, North Carolina M. J. 18:311, 1957.
4. Kirsner, J. B., Ford, H., and Kassriel, R. S.: Current Status of Anticholinergic Drugs in Peptic Ulcer, M. Clin. North America March, 1957.
5. Lichstein, J.: Pro-Banthine in the Treatment of Peptic Ulcer, Am. J. M. Sc. 232:156, 1956.
6. Roth, J. L. A., Wechsler, R. L., and Bockus, H. L.: Hazards in the Use of Anticholinergic Drugs in the Management of Peptic Ulcer Disease, Gastroenterology 31:493, 1956.
7. Texter, E. C., Baylin, G. J., Legerton, C. W., and Ruffin, J. M.: Effects of a New Cholinergic Blocking Agent (S.K.F.—1637) on Gastric Motor and Secretory Activity, Am. J. M. Sc. 244:612, 1952.
8. Kirsner, J. B., and Palmer, W. L.: Newer Gastric Antisecretory Compounds, J.A.M.A. 151:798, 1953.
9. Legerton, C. W., Texter, E. C., and Ruffin, J. M.: The Mechanism of Relief of Pain in Peptic Ulcer by Banthine, South. M. J. 45:310, 1952.
10. Ruffin, J. M., Baylin, G. J., Legerton, C. W., and Texter, E. C.: Mechanism of Pain in Peptic Ulcer, Gastroenterology 23:252, 1953.
11. Hightower, N. C., and Gambill, E. E.: The Effects of Banthine on Pain and Antral Gastric Motility in Patients with Duodenal Ulcer, Gastroenterology 23:244, 1953.
12. Lepore, M. J., Golden, R., and Flood, C. A.: Oral Banthine, An Effective Depressor of Gastrointestinal Motility, Gastroenterology 17:551, 1951.
13. Kirsner, J. B.: Anticholinergic Compounds in Peptic Ulcer, (Ed.) Gastroenterology 32:953, 1957.
14. Sun, D. C. H., and Shay, H.: Optimal Effective Dose of Anticholinergic Drugs of Peptic Ulcer Therapy, A.M.A. Arch, Int. Med. 97:442, 1956.
15. Kirsner, J. B., and Palmer, W. L.: Certain Problems of the Medical Management of Peptic Ulcer, South. M. J. 49:817, 1956.

Discussion (Abstract)

Dr. William L. Alsobrook, Nashville, Tenn. The mechanism of the production of pain in peptic ulcer has been debated for several years. A considerable amount of evidence has accumulated that abnormal motility causes pain rather than simple acid production. This has been found by several investigators using I.V. preparations of anticholinergic drugs. It has been found that in many cases pain can be ablated almost immediately by I.V. anticholinergic drugs although the acid content of the stomach remains high.

Since the advent of anticholinergic drugs, numerous preparations have been introduced by pharmaceutical houses, and the relationship between the chemical structure and the pharmacologic aspects of the drug has been considerably advanced. This is true not only of the anticholinergic drugs, but of antispasmodics, antihistamines, the local anesthetics, and the tranquilizer drugs. All of these drugs share a rather intimate and fundamental inter-relationship as far as their pharmacologic mechanism is concerned. There is work proceeding at this time using an almost pure anticholinergic drug as a tranquilizer.

The case for abnormal motility being the cause of pain in ulcer is well documented. The use of a pure ganglionic blocking agent such as tetra-ethyl-ammonium chloride will relieve the pain of peptic ulcer immediately. Banthine and similar drugs relieve the pain and they also have been found to have a central effect. For instance, the pain of peptic ulcer can be relieved by tetra-ethyl-ammonium chloride although the pain of increased distention of the stomach cannot be relieved, while Banthine will relieve both the pain of ulcer and pain which is produced by distention of the stomach. This action cannot be attributed to interference with transmission at the autonomic ganglia because tetra-ethyl-ammonium chloride is a much more potent ganglionic blocking agent than Banthine. Another central effect of Banthine has been noted by anesthesiologists using intravenous Banthine for its antisecretory effect. They have noted that patients who receive Banthine intravenously as a preoperative medication not only have much less secretions but as a rule require considerably less anesthesia.

It has been found that the antisecretory effect of the anticholinergic drugs when taken orally is variable and it may be that nearly all of the results achieved by these drugs are through its anti-motility effect. In a re-appraisal of the role of these drugs in the treatment of duodenal ulcer several questions are raised. Since probably these drugs have the greatest effect on motility, how much is contributed toward healing the ulcer since, with motility diminished, there is a prolonged gastric phase to the digestive process with a continuation of the acid pepsin secretion. In our institution we have used the anticholinergic drugs only in uncomplicated cases of ulcer in which pain has been the prinicipal symptom. We have not embarked upon any long-range therapy particularly from a preventive aspect, feeling that the main problem in duodenal ulcer therapy is neutralization of the acid pepsin and have continued patients on antacids and frequent feedings. As Dr. Legerton and Dr. Ruffin pointed out several years ago, these drugs probably do not prevent the recurrence of an ulcer. One major side-reaction in our experience to the use of these drugs is based upon its action of paralysis of the motor function of the stomach. In patients who have symptoms of obstruction, however mild, we have found that the anticholinergic drugs only increase the obstructive symptoms, and for the hospitalized patient with severe ulcer symptoms, these are not routinely employed. It might be said parenthetically here that barbiturates have been used many years before these drugs appeared and with very satisfactory results; recent work has now shown that the barbiturates do have anticholinergic action.

Limbic Tumors*

JEROME L. BYERS, M.D.,† *Dallas, Tex.*

Precancerous tumors of the epithelium of the eye are relatively uncommon. Their early recognition, however, is important since their removal is often a matter of cure.

WITHIN A RELATIVELY SHORT TIME in the last year we were privileged to see a number of tumors involving the limbic area of the eye. These cases stimulated the presentation of this paper to review the clinical and histopathologic features of the more common epithelial tumors of the limbus.

Because of the limitation of time only epithelial tumors of the limbus will be discussed, excluding pigmented tumors, dermoid tumors, lymphomas, and the rare vascular tumors.

As occurs elsewhere in the body, in areas of epithelial transition and at sites of chronic irritation, epithelial tumors are found to be located at the limbus most often, usually on the temporal side in the palpebral aperture.

Ash,[1] in 1948, reported 1,120 cases of epibulbar tumor taken from the files of the Armed Forces Institute of Pathology. Three hundred and forty-six were epithelial tumors. Of these, almost 90% (311 cases) occurred in Caucasians and only 10% (35 cases) in Negroes. There were almost five times as many squamous cell carcinomas in males as in females.

It is generally agreed that the incidence of these tumors seems to be significantly higher in individuals who spend much of their time outdoors where they are exposed to such factors as heat, dryness, irritating dusts and ultraviolet irradiation.

Between the ages of 50 and 80 years there is a sharp rise in the incidence of these lesions. Only rarely do they occur below the age of twenty.

Ash divided epithelial tumors into three groups:

1. Hyperplasia of normal conjunctival or corneal epithelium to the squamous type. (This type of transition may occur in any inflammatory process. Into this category he placed leukoplakia and Bowen's tumor.)

2. Papilloma formation.

3. Frank squamous or basal cell carcinoma which may develop from either of the first two groups.

Clinical Considerations

Leukoplakia. Clinically, an area of leukoplakia is flat, white and superficial in contrast to a pingueculum which is yellow and subepithelial. This whiteness is due to a combination of relative avascularity and opacification of the hyperplastic and metaplastic cells of the leukoplakia. Thygeson[2] in discussing Swan's paper in 1948 noted that the Bitot's spot must be distinguished from leukoplakia, since it also is localized frequently at the temporal limbus. Bitot's spot, a hyperkeratotic lesion of early vitamin A deficiency, is characterized by its triangular shape and its glistening appearance early, which later becomes dull and white. Many xerosis bacilli can be demonstrated with a gram stain of scrapings taken from this lesion. Unlike the other dyskeratotic lesions, Bitot's spot will respond to vitamin A administration.

Ash and Wilder[3] described the histopathologic features of leukoplakia as being "acanthosis, hyperkeratosis, and dyskeratosis," and representing in varying degrees a subepithelial chronic inflammatory reaction.

Swan[2] suggests careful study of the leukoplakic lesion with a slit-lamp for the development of a capillary network on a portion of the lesion. He found this beginning vascularity to be a reliable sign of early malignant change, more so, even, than increasing size and loss of flatness of the lesion.

Epithelioma. As the change to frank malignancy takes place, the superficial flat white

*Read before the Section on Ophthalmology and Otolaryngology, Southern Medical Association, Fifty-Second Annual Meeting, New Orleans, La., November 3-6, 1958.

†From the Department of Ophthalmology, Tulane Medical School, New Orleans, La.
Trainee (1957-1958), Division of Neurological Diseases and Blindness, National Institutes of Health, Washington, D. C.

plaque becomes a fleshy-colored, firmly fixed squamous cell epithelioma which usually exhibits a single artery and accompanying vein feeding into the tumor. With the biomicroscope the surface of the tumor can be seen to be lobular, with small vessels forming a characteristic bud at the apex of each lobule. Of course, if the carcinomatous changes take place in a papilloma, the tumor will have the characteristic cauliflower appearance of the papilloma.

Early there is only superficial extension over the cornea, Bowman's membrane offering a resistant barrier to stromal invasion until the tumor has advanced well over the cornea.

Necrosis of a portion of the tumor indicates stromal involvement and the patient may be mistakenly treated for an inflammatory or traumatic corneal ulcer. One of Swan's cases developed a descemetocele followed by spontaneous perforation. Noteworthy, was the relative lack of pain seen with necrotic malignant corneal ulcers as compared to the pain of ulcers of similar size of infectious origin.

Histopathologically the epithelioma is characterized by typical epithelial pearls or cell nests surrounded by prickly and polygonal cells which, in turn, are adjacent to cuboidal and cylindrical-shaped cells. The cell nuclei have a variety of sizes and shapes. A considerable inflammatory reaction is usually present. As was mentioned, invasion of the corneal stroma occurs late, since Bowman's membrane serves as a barrier to deep stromal spread of the tumor.

Bedell,[4] in 1946, reported a case of epidermoid carcinoma which started at the limbus 18 years before it completely covered the cornea and yet histologically had not yet invaded the stroma, although Bowman's membrane was destroyed over a large area.

The basal cell type of epithelioma occurs rarely at the limbus as compared to its occurrence on the eyelids and other skin surfaces. Iliff[5] reported one basal cell epithelioma in 9 cases of carcinoma of the limbus. In a series of 48 epitheliomas reported by Ash and Wilder[3] there was only one basal cell type.

Because of the low grade of malignancy as compared to tumors of this type elsewhere and because deep corneal invasion and scleral invasion occur late, surgical excision of the early lesion is advocated by Ash,[1] Iliff,[5] Swan and others[2,6] rather than the more radical procedure of enucleation of the eye, or of exenteration of the orbit; these more radical procedures should be reserved for late invasive tumors and for recurrences.

In simple surgical excision of the epithelioma the extent of surrounding tissue which must be excised by the surgeon should be predetermined by slit-lamp evaluation, in order to eradicate as much outlying altered epithelium as possible. The metaplastic epithelial cells between the tumor mass and normal epithelial cells serve as a source for regrowth of the tumor and, therefore, these cells must be removed at time of operation if recurrence is to be prevented. Locke[7] reduced the number of recurrences by carefully removing one millimeter of normal epithelium surrounding the lesion.

Limbic epitheliomas are uniformly radiosensitive. However, Swan[2] believes that, unless there has been appreciable conjunctival or corneal involvement, postoperative irradiation should be held in reserve for recurrences. By contrast both Reese[8] and Iliff[5] have observed a relatively high rate of recurrence and feel that postoperative irradiation is thereby justified after the initial surgical excision, with systematic follow-up examinations to immediately eradicate any small recurrence.

Among 48 cases of limbic carcinoma reported by Ash and Wilder,[3] only one death could be attributed to the tumor. After simple excision in 23 cases, only 2 required additional surgical treatment for complete eradication. Enucleation was performed in 23 cases. In Iliff's series of 9 cases, 4 tumors were removed by simple surgical excision followed by irradiation, and 5 were removed by surgery alone. There was recurrence in only one case where surgical treatment alone was used. In this instance exenteration of the orbit was necessary as a final procedure.

Papilloma. A pedunculated cauliflower-like papilloma may occur at the lid margins, caruncle, and at the limbus in the older age group. When this tumor arises at the limbus it may spread out over the cornea or back over the conjunctiva to the cul-de-sac. In 28 patients with papilloma of the limbus reported by Ash and Wilder, 25 were of the

epithelial type and 3 of the conjunctival type. Only one recurred in 18 cases treated by local excision. Because of extensive corneal involvement, 8 were enucleated as the primary mode of treatment. In a later paper, Ash[1] reported a 27% recurrence in 138 patients with papillomas and suggested that where only the grossly evident papillomatous lesion was excised at operation, surrounding unrecognized epidermidalization of the conjunctiva and corneal epithelium served as a focus for recurrence. Although the papilloma is a relatively benign tumor, alterations of its epithelium into frank malignancy is possible. Eight of 48 frank carcinomas reported by Ash and Wilder were of the papillary squamous-cell type. Thus, clinically, one may be hard pressed to differentiate a benign papilloma from one which has undergone malignant change.

Reese[8] advises excision of these lesions flush with the surface of the limbus. Although papillomas are highly sensitive to irradiation, he feels that exposure of the eye to irradiation hazards is not justified in these cases. Iliff suggests cautery of the central vessel at the base of the tumor to make recurrence less likely. He prefers beta radiation.

Bowen's tumor. McGavic[9] in 1942, reported the first 5 cases of intra-epithelial epithelioma or so-called Bowen's disease of the cornea and conjunctiva, 30 years after the original description of the skin lesion by Bowen. Since then there have been numerous reports in the literature. Locke,[7] in 1956, reported 12 cases from the Institute of Ophthalmology, Presbyterian Hospital, New York in addition to those of McGavic. He also reported no recurrence six and one-half years after simple excision of a diffuse Bowen's lesion by Wise.[10] This lesion had covered the entire cornea, but only a small portion of bulbar conjunctiva adjacent to the limbus was involved. Of this group of 18 cases there were only 3 instances of malignant change of the Bowen's tumor to the squamous cell type of tumor. However, Reese[11] considers Bowen's tumor to be potentially malignant and that if it is not completely removed may metastasize.

Clinically, the lesions may be "slightly elevated, diffuse, sometimes multiple, highly vascularized patches of reddish-gray, gelatinous tissue"[9] and can be mistaken for pannus formation, Mooren's ulcer, filtering cicatrix of the cornea, epithelial dystrophy of the cornea, and pterygium. So, although the lesion can be suspected clinically, a definite diagnosis can only be made microscopically.

Histopathologically, the epithelium is thickened, with proliferation of the basal cells which have lost their palisade-like arrangement. However, the basement membrane remains intact and the basal cells remain in place as a definite layer. Characteristically, an abrupt transition between the normal and hyperplastic tissue takes place. There is a marked variation in size, shape and staining qualities of the cells, with formation of so-called multiple nuclei clumped together or of a cell containing a very large single nucleus. Mitotic figures are common. There is a moderate chronic inflammatory reaction present underneath the epithelium, and occasionally this inflammatory reaction may overshadow the hyperplastic nature of the lesion clinically.

In contrast to the other epitheliomatous lesions of the cornea and conjunctiva, Bowen's tumor is not very sensitive to irradiation and, indeed, McGavic,[12] in a discussion of Swan's paper, suggests that both beta and grenz rays may stimulate rather than destroy the lesion. Dosages of x-ray and radium which will destroy the tumor are larger than can be used safely around the eye. The treatment of choice is complete surgical excision. If the lesion is extensive enough to cover the conjunctiva, Reese recommends enucleation.

Summary

In conclusion, leukoplakia, papilloma and Bowen's tumor must be considered precancerous tumors which, though slow growing, can eventuate into squamous and, rarely, into basal cell carcinoma. With the exception of leukoplakia and Bowen's tumor, these epitheliomatous lesions are radiosensitive and may be removed by the various methods at our disposal; however, it is generally agreed that the treatment of choice is surgical removal of the lesion with a relatively wide margin of normal tissue. It is to be emphasized that Bowen's tumor may be aggravated by radiation therapy. Clinically, differential diagnosis is difficult in many instances even for the experienced physician who must leave the final diagnosis to the pathologist.

References

1. Ash, J. E.: Epibulbar Tumors, Am. J. Ophth. 33:1203, 1950.
2. Swan, K. C., Emmens, T. H., and Christensen, L.: Experiences with Tumors of the Limbus, Tr. Am. Acad. Ophth. 52:458, 1948.
3. Ash, J. E., and Wilder, H. C.: Epithelial Tumors of the Limbus, Am. J. Ophth. 25:926, 1942.
4. Bedell, A. J.: Epidermoid Carcinoma of the Cornea, Am. J. Ophth. 29:864, 1946.
5. Iliff, C. E.: Diagnosis and Treatment of Tumors of the Head and Neck, by Ward, G. E., and Hendrick, J. W. Baltimore, Williams & Wilkins Co. (Chap. XIV), 1950.
6. Samuels, B.: Tumors of Conjunctiva and Lids, Arch. Ophth. 26:789, 1941.
7. Locke, J. C.: Bowen's Disease of the Cornea and Conjunctiva, Am. J. Ophth. 41:801, 1956.
8. Reese, A. B.: Tumors of the Eye. New York, Paul B. Hoeber, Inc., 1951, p. 23.
9. McGavic, J. S.: Intraepithelial Epithelioma of the Cornea and Conjunctiva (Bowen's Disease), Am. J. Ophth. 25:167, 1942.
10. Wise, G. A.: A Case of Bowen's Disease of the Cornea, Am. J. Ophth. 26:167, 1943.
11. Reese, A. B.: Tumors of the Eye. New York, Paul B. Hoeber, Inc., 1951, p. 33.
12. McGavic, J. S.: Discussion of Experiences with Tumors of the Limbus, by Swan, K. C., Emmens, T. H., and Christensen, L., Tr. Am. Acad. Ophth. 52:468, 1948.

Meet Us in Atlanta, Ga.

November 16-19, 1959

for

SMA's 53rd Annual Meeting

Contributions of Intraluminal Pressure Measurements to our Understanding of Esophageal Disorders*

JOSEPH H. STICKLEY, M.D., *Atlanta, Ga.*, E. CLINTON TEXTER, JR., M.D., and CLIFFORD J. BARBORKA, M.D., *Chicago, Ill.*, HUBBARD W. SMITH, M.D., *Greeley, Colo.*, and GASTON VANTRAPPEN, M.D.,† *Louvain, Belgium*

Much more is to be known of the relationship of changes in motility of the esophagus to diseased conditions of this organ. Studies of this type extend our knowledge in this area.

THE TRANSPORT OF SWALLOWED MATERIAL from the pharynx to the stomach by reflexly coordinated phasic motor activity is the major function of the esophagus. Although the mechanism of swallowing has been studied from the time of Hippocrates, there has been a tendency on the part of physicians to look upon the esophagus as merely a flaccid tube through which food and drink pass to reach the stomach. Until recently, investigators have been inclined to dismiss, as being simple and uncomplex, the esophageal contribution to swallowing. This narrow point of view ignores the work of the earlier physiologists and, in particular, the results of recent investigations of esophageal motility.

The experimental physiologist, Magendie,[1] in 1822 divided deglutition into three stages, oral, pharyngeal, and esophageal. His work has served as a springboard for subsequent investigations. Kronecker and Meltzer,[2] in 1883, opened the way for accurate investigation of esophageal motility by using small intra-esophageal balloons connected to external manometers to obtain kymographic records of the pressure variations that accompany swallowing. Another important technic for the study of esophageal motility was devised by Cannon and Mosher[3] when they published their fluoroscopic observations on the movements of the esophagus in 1898. Despite the fact that the basic technics for the study of esophageal motility have been available for some years, the esophagus has remained a sort of "no man's land" divided between the otolaryngologist, the roentgenologist, and the thoracic surgeon.[4]

Lerche,[5] in 1950, published a small monograph, "The Esophagraph and Pharynx in Action," based upon detailed study of 100 anatomic specimens. He reaffirmed that there is a short segment, with distinct characteristics which connects the esophagus to the stomach, which he termed the "gastroesophageal vestibule." Concurrently, new methods were developed for studying motor function of the esophagus, including stable pressure-sensitive transducers for recording intraluminal pressures,[6] *in vivo* transducers,[7] radio telemetering capsules,[8] highspeed cinefluorography,[9,10] and the combination of simultaneous cineradiographic or fluorocinematographic and manometric observations.[11-15]

During the past five years, more than 100 manometric studies of esophageal motility have been carried out in the laboratory and the manometric observations have been combined with simultaneous fluorocinematography in approximately half of these studies.[15]

---

*Read before the Section on Gastroenterology, Southern Medical Association, Fifty-Second Annual Meeting, New Orleans, La., November 3-6, 1958.

†From the Gastroenterology Unit, Department of Medicine, Veterans Administration Research Hospital and Passavant Memorial Hospital, Northwestern University Medical Center, Chicago, Ill.

This investigation was supported in part by a research grant (RG4633-C2-Physiology) National Institutes of Health, Public Health Service, and by grants from the Smith, Kline & French Foundation, the Lakeland Foundation, the James Picker Foundation, G. D. Searle & Company, A. H. Robins Co., and the Gastroenterology Research Fund.

Dr. Vantrappen was Trainee in Gastroenterology, National Institute of Arthritis and Metabolic Diseases, 1957-1958. James Picker Foundation Fellow in Radiological Research, recommended by the Committee on Radiology, National Academy of Sciences—National Research Council, 1958-1959. Present address: Universiteitsklinieken, St. Rafael, Louvain, Belgium.

From these observations and similar studies at other institutions, it has been possible to formulate some concepts about normal esophageal motor function and its derangement in disease states.[16-27] Some esophageal disorders result in characteristic intraluminal pressure patterns which may be of help in diagnosis and treatment.

Method

Intraluminal pressures were recorded using multiple fluid-filled catheters having an internal diameter of 1.52 mm. and a length of 120 cm. Three catheters were arranged with their distal tips in tandem fashion 3 to 5 cm. apart, thus permitting recording of pressures from three areas simultaneously. The catheters were connected to external transducers (Statham unbonded strain gauges P-23D) and a four-channel carrier amplifier recorder (Sanborn Polyviso 150). The pressures were recorded directly on heat-sensitive paper and were also transmitted to an oscilloscope (Sanborn electronic switch and visoscope).

Normal subjects and patients with esophageal disorders were studied. The patients were placed in the prone right anterior oblique position after the catheters had been passed through the mouth into the stomach. The catheters were pulled back centimeter by centimeter until the characteristic pressure changes at the diaphragmatic hiatus could be recorded. The pressures in the high-pressure zone above and below the esophageal hiatus were studied. Resting pressures were measured at each centimeter interval, as were the pressure alterations in response to a single dry swallow (swallowing of air and a small amount of saliva) and the pressure alterations in response to a swallow of 10 ml. of a suspension of barium sulfate. The "pullback" technic was continued at 1 cm. intervals through the body of the esophagus and through the pharyngoesophageal sphincter. The effects of distention of the esophagus, as well as the action of autonomic-acting drugs, were studied in some patients.

Fluoroscopy and simultaneous fluorocinematography were used to correlate the pressure changes accompanying deglutition with the roentgen appearance of the esophagus. The General Electric TV-X developmental fluorocinematographic unit was employed, using initially the 8 and later the 12 inch photoconductive camera. The x-ray-induced pattern was scanned by an electron beam and the resultant electrical signal amplified and displayed using closed circuit television. A recording camera (modified Auricon) was synchronized to the image on the viewing kinescope. The low roentgen output (1 to 3 roentgens per minute at the tabletop) permitted detailed observations within the accepted limits of radiation safety. The pressure complexes were superimposed on the fluorocinematographic film by means of a superimposition attachment. The details of the technic have been reported previously.[13-15]

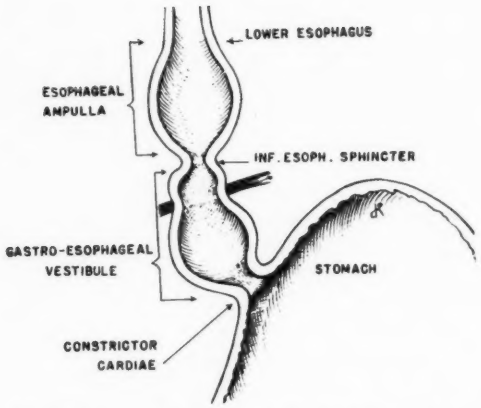
Normal Function of the Esophagus

The normal sequence of events of swallowing have been described.[28,29] and will be reviewed only briefly.

During the first stage of swallowing the material to be swallowed is passed from the mouth to the pharynx. The second, or pharyngeal stage, is brief but complicated.[9,10,29] The superior pharyngeal constrictor muscle contracts and a rapid peristaltic wave is generated which sweeps the bolus ahead of it. The third stage of deglutition begins after the cricopharyngeous muscle has opened which permits the bolus to enter and traverse the esophagus. The relative contributions of buccal-pharyngeal pressure, esophageal peristalsis and gravity on moving the bolus through the esophagus vary, depending upon the nature of the bolus and the position of the patient.

At the junction of the esophagus and the pharynx above and the stomach below, physiologic sphincteric mechanisms are present.[29] The upper end of the esophagus is closed by a true anatomic sphincter, the cricopharyngeous muscle. From here, the esophagus follows a gentle curve downward, expanding in the distal intrathoracic portion to form a small bulbar dilatation, 2 to 3 cm. in length, termed the esophageal ampulla. The ampulla ends 1 to 2 cm. above the hiatus, with a physiologic narrowing of the lumen which Lerche termed "the inferior esophageal sphincter." The esophagus is joined to the stomach by the gastroesophageal vestibule which measures 2 to 5 cm. in length and extends through the diaphragmatic hiatus, terminating in another constriction, the constrictor cardiae (Fig. 1).

FIG. 1



Schematic diagram of anatomy of the distal esophagus according to Lerche. Ref. 5 (reprinted by permission from Hightower, N. C., Jr., Dis. Chest 28:150, 1955).

Fyke and Code[23] have demonstrated that the superior end of the esophagus is closed off from the pharynx under resting conditions by a tonic contraction of the pharyngeal sphincter. The position of this sphincter corresponds exactly to the band of high resting pressure found at the junction of the pharynx and the esophagus.[23,29] Muscular elements, derived directly from the esophagus, also probably contribute to closure of the upper end of the esophagus.[29]

The correlation between anatomic structures and physiologic phenomena at the distal end of the esophagus is not as exact as at the upper end of the esophagus. The zone of high pressure normally present at the gastroesophageal junction has all the physiologic characteristics of a sphincter.[25] However, no well-defined anatomic sphincter can be delineated to correspond with the physiologic sphincteric mechanism, although the zone of high pressure corresponds in location to the area of the gastroesophageal vestibule.

The gastroesophageal vestibule exhibits physiologic and pharmacologic characteristics different from those of the esophagus. The primary peristaltic wave stops at the level of the vestibule and this zone appears to act as a sphincter. However, muscular relaxants, ganglionic blocking agents, and subperitoneal injections of local anesthetics into the area of the vestibule and gastric cardia do not result in relaxation of this area and subsequent gastroesophageal reflux.[30]

Despite the somewhat inconclusive anatomic evidence for a sphincter at the gastroesophageal junction, the physiologic data indicate that the high pressure zone represents a physiologic sphincter which is tonically contracted in the resting state and relaxed upon swallowing.[27] The high pressures in this zone are also abolished in response to distention of the esophagus.[15,31,32] The mechanisms responsible for maintaining the tonic state of this zone at rest are not clear, although the data suggest that this response is related to the independent motor activity of the gastroesophageal vestibule. This conclusion is supported by cineradiographic studies.[15,33]

The pressure complex in response to swallowing is usually characterized by four components,—an initial small negative dip, a sudden positive wave, a gradually rising positive wave or a plateau, and a final positive peak. The large positive peak which terminates the complex is recorded as the peristaltic traction sweeps over the open tip of the catheter. The final component of the primary peristaltic wave is a lumen-obliterating contraction, 4 to 8 cm. in length, which moves downward at a rate of 2 to 4 cm. per second.[29]

Three types of esophageal contractions may be recorded from normal individuals: the primary peristaltic wave; secondary peristaltic waves resulting from distention of the esophagus; and tertiary or nonperistaltic esophageal contractions. The latter occur spontaneously, or in response to swallowing or distention in the lower two-thirds of the esophagus, and account for the radiologic appearance of curling, corkscrew esophagus or pseudodiverticula. Nonperistaltic contractions are more common in patients past middle age.[34,35] Nonperistaltic esophageal activity, when marked, may result in dysphagia.[15,29]

Motor Function of the Esophagus in Disease States

Achalasia. Achalasia, or cardiospasm, is a generalized disorder of motility which involves most of the esophagus.[17,36] A characteristic pattern of esophageal motility is found in patients with achalasia. The primary peristaltic wave travels only to the level of the suprasternal notch.[37] The resting pressures of the esophagus are usually at atmospheric level but they may be higher than normal due to retained fluid and secretions. The normal

high pressure zone between the pharynx and the esophagus is present.

Normal complexes of deglutition are not seen in patients with achalasia, although occasionally waves may be recorded which grossly resemble the normal swallowing complex.[17] Pressure waves unrelated to deglutition and multiple phasic contractions in response to a single swallow have been observed.[17] Secondary motor activity as a result of fluid distending the esophagus may also be recorded.

The normal decrease in pressure at the esophagogastric junction upon swallowing is absent in patients with achalasia. The resting pressures in this zone are normal in patients who have been treated by dilatation although higher than normal pressures at the esophagogastric junction have been measured from untreated patients[28] (Fig. 2).

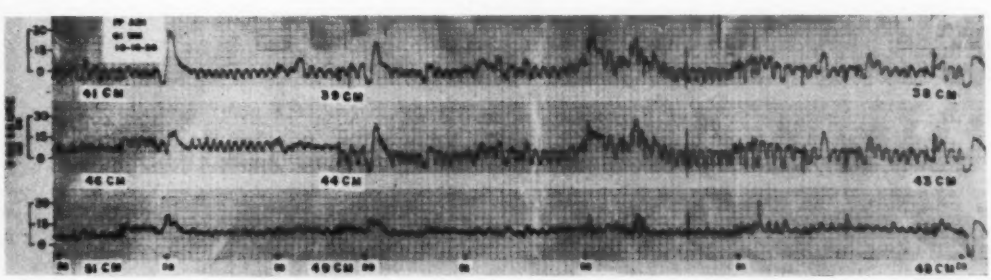
A marked increase in response to parenterally administered cholinergic agents is present in patients with achalasia. Intraluminal pressures in excess of 100 mm. of Hg. have been recorded simultaneously with tetanic contractions which involve simultaneously one-fourth to three-fourths of the lower esophagus.[36] The strong tetanic contraction has been interpreted as representing the hypersensitive reaction of the postganglionically denervated smooth muscle to the neuropharmacologic agent.[29]

Because of the lack of coordinated propulsive motor activity of the esophagus, ingested material will leave the esophagus only when the barrier offered by the tone of the inferior esophageal sphincter is overcome by pressure within the esophagus. Two factors are involved in esophageal emptying,—the height of the column within the vertical esophagus and the pressure generated by contractions of the entire esophagus.[28,36] Since there are no measures capable of restoring normal esophageal propulsive activity, treatment of patients with achalasia is based upon decreasing the resistance at the cardioesophageal junction by divulsion of the vestibule either by brusque dilatation or following the Heller esophagomyotomy.[38] Following a properly performed dilatation or an esophagomyotomy procedure, the supradiaphragmatic portion of the high pressure zone, corresponding to the inferior esophageal sphincter, is abolished, but the infradiaphragmatic segment remains (Fig. 2). It is important that this segment of the high pressure zone be preserved to prevent subsequent reflux of gastric contents into the esophagus.

Diffuse spasm of the esophagus. This is a syndrome comprised of intermittent dysphagia and substernal pain.[39-41] Diffuse spasm of the esophagus is characterized by a distinct pattern of abnormal motility.[15,28,42] Roentgenologically, a diffuse spasm is associated with an abnormal radiologic appearance of the esophagus, described as curling or corkscrew esophagus.[34,41,43]

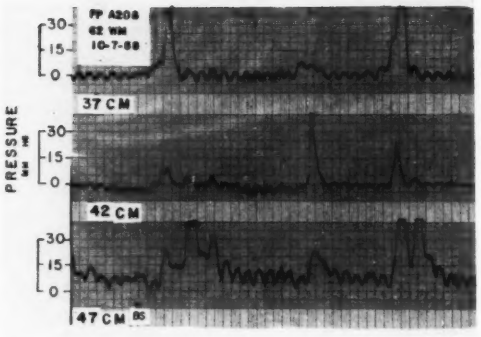
The resting pressures of the esophagus in patients with diffuse spasm are usually normal. The high pressure zone, corresponding to the pharyngoesophageal sphincter, is normal. Peristaltic waves are usually normally propagated in the upper third of the esophagus. Below this, the primary wave blends with, or is replaced by, abnormal rises in pres-

FIG. 2



Intraluminal pressure tracing from a 61 year old patient with achalasia utilizing the pull-back technic with 3 catheters 5 cm. apart. Dry swallows are indicated by capital DS, barium swallows by capital BS, and a deep breath by capital DB. The onset of the swallow or deep breath is indicated by the arrow. The paper speed is 2.5 mm. per second. No normal deglutition complexes are seen. A high pressure zone was recorded for 3 cm. below the diaphragm from 51 to 48 cm. from the incisors but no high pressure zone could be recorded above the diaphragm. This patient had previously been treated by use of the Mosher dilator. The relation of the catheters to the diaphragmatic hiatus can be determined by the direction of the respiratory complexes. The pressures are given in millimeters of mercury.

FIG. 3



Intraluminal pressure tracings from a 62 year old white man with diffuse spasm and a penetrating duodenal ulcer. The location of the catheters is noted according to their distance from the incisors. The paper speed was 2.5 mm. per second. The slide shows a barium swallow followed by spontaneous non-peristaltic motor activity.

sure which have distinct characteristics. The contractions are premature, repetitive, and the pressures are simultaneous rather than peristaltic.[42] The pressure waves are of higher amplitude and longer duration than are the normal deglutition complexes.[15] Abnormally high pressures in the high pressure zone at the inferior esophageal sphincter have been recorded, which may persist for as long as eleven minutes.[15] These high pressures effectively prevent esophageal transport despite repeated attempts at swallowing (Fig. 3).

Some patients with diffuse spasm have been treated by a myotomy procedure in which the muscular coat of the esophagus is sectioned in longitudinal fashion overlying the area of persistent high pressure.[44] It is too early to determine whether this procedure will result in lasting benefit.

Scleroderma. Scleroderma is a disorder characterized by sclerodermatous infiltration of the esophagus and other portions of the body. A characteristic pressure pattern may be recorded from patients with scleroderma. Deglutition is abnormal. Roentgenologically it can be observed that the primary peristaltic wave is transmitted only to the level of the suprasternal notch. Normal esophageal motility is absent below this level.[45,46] When patients are standing barium passes through the esophagus without delay. In the supine position, the absence of peristalsis results in almost complete retention of barium within the esophagus.

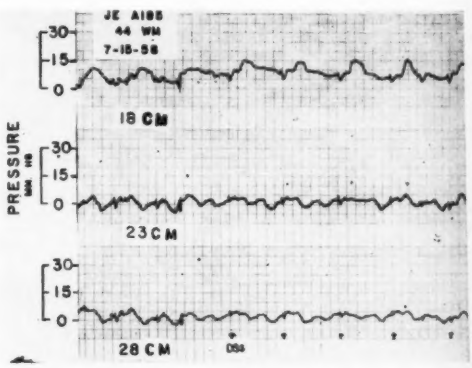
Normal or increased resting pressures are found in the esophagus. The superior pharyngeal constrictor contracts normally and the primary peristaltic wave passes through the high pressure zone at the pharyngoesophageal junction. Few primary waves reach the lower esophagus in patients with scleroderma[24] (Fig. 4). Either no motility is recorded in response to swallowing or a pattern of incoordinated contractions may be evident (Fig. 5).

The high pressure zone at the inferior esophageal sphincter is absent above the diaphragm and in some cases no evidence of a high pressure zone may be observed infradiaphragmatically (Fig. 6). The pressures in this zone may be affected by respiration, being decreased at end expiration and increased at end inspiration.[46]

The low and ineffectual propulsive wave explains the almost complete dependency upon gravity for esophageal transport in patients with scleroderma. The end results of these abnormalities is the loss of contractile power of the esophagus which extends to the gastroesophageal sphincter. Inasmuch as this segment, which should normally be closed, remains patulous, gastric contents can reflow into the esophagus and the esophagus is powerless to expel them into the stomach. Reflux esophagitis is then superimposed upon the underlying disease, namely, sclerodermatous infiltration of the esophagus.

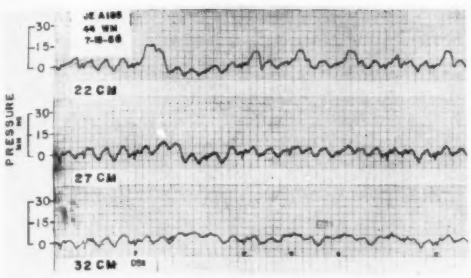
The motility patterns of the esophagus are

FIG. 4



Intraluminal pressure tracing from a 44 year old man with scleroderma. During the first section of the tracing, the upper catheter was below the pharyngoesophageal junction but on withdrawal to 18 cm. from the incisors, the upper catheter can be seen in the pharyngoesophageal junction. Repeated dry swallows are indicated by the arrows. Paper speed was 5 mm. per second.

FIG. 5



Intraluminal pressure tracing from a 44 year old white man with scleroderma. Proximal catheter is located 22 cm. from the incisors, slightly below the pharyngoesophageal junction. Some indication can be observed of swallows from the upper tracing as indicated by the arrows but no evidence of deglutition complex is noted in the two more distally located catheters. Paper speed was 5 mm. per second.

sufficiently distinct to be of real value in the diagnosis of scleroderma. Although little can be done to influence the sclerodermatous infiltration of the esophagus, the knowledge that the lower esophageal sphincter is incompetent can be used to direct treatment toward the accompanying erosive esophagitis.

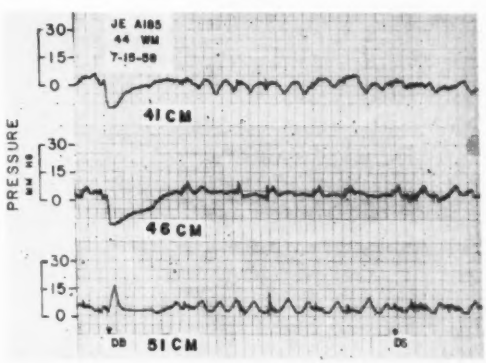
Hiatal hernia. The normal relationships at the esophagogastric junction are disrupted in patients with herniation of the stomach through the hiatus. This has provided an excellent opportunity for the radiologic and manometric study of this segment. Abnormal motor activity is observed in patients with hiatal hernia. Roentgenologically, esophageal function may appear relatively normal. Frequently, abnormalities may be observed consisting of either delayed transport of barium or frequent nonperistaltic motor activity.

The resting pressures in the esophagus are normal in patients with hiatal hernia. The primary deglutition complex is normally propagated in the pharynx and transmitted through the pharyngoesophageal junction and the upper two-thirds of the esophagus. When the catheters are located just supradiaphragmatically, deglutition complexes of low amplitude and long duration may be recorded.[26,47] Nonperistaltic activity of the esophagus just above the level of the hernia is frequent.

Measurement of intraluminal pressures does not always lead to recognition of the high pressure zone corresponding to the inferior esophageal sphincter in patients with hiatal hernia. When a portion of the stomach is herniated into the thorax, the resting pressures of the gastroesophageal high-pressure zone may be equal to those of the hernia, the resting pressures in the hernia being higher than those either at the esophagus or the fundus of the stomach. The gastroesophageal sphincter can then be identified by its characteristic response to swallowing. If no hernia is demonstrable at the time of study, the high pressure zone is located either normally or displaced slightly upward. The resting pressures in the high pressure zone may decrease with inspiration and increase with expiration. In some patients the respiratory variations in the herniated stomach may be noted to be out of phase with those recorded from the esophagus above and the subdiaphragmatic stomach below.[42]

The high pressure zone may be located higher than normal in patients with small sliding hiatal hernias. An area corresponding to Lerche's description of the gastroesophageal vestibule may be located in the thorax. Using the technic of repeated swallowing, Wolf[33] has shown that barium is often retained in the distal esophagus and in the small hernial sac, which has made it possible to visualize the proximal and distal margins of an unfilled, or contracted segment. This segment, measuring 2 to 3 cm. in length, is present between the tubular esophagus and the hernial sac and may not relax for several seconds. It then subsequently fills out as a unit. From its location, length, and appear-

FIG. 6



Intraluminal pressure tracing from a 44 year old white man with scleroderma. The lower catheter is located at the diaphragmatic hiatus. No evidence of a high pressure zone was observed either above or below the hiatus. The response to respiration is shown at the arrow labelled capital DB and a dry swallow at the arrow capital DS. Paper speed was 5 mm. per second.

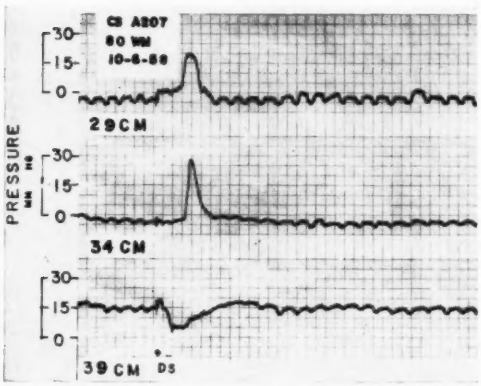
ance when distended, this segment appears to correspond to the gastroesophageal vestibule (Fig. 7).

Alterations in the pressure tracing may be of value in the diagnosis of hiatal hernia. Studies of the gastroesophageal junction in postoperative patients may give some indication as to the degree to which normal anatomic arrangements can be restored by the surgeon. Studies to date have demonstrated that the abnormalities of the deglutition complex and the inferior esophageal sphincter persist following surgical repair.

Other disorders. The term "chalasia" has been proposed for the disorder noted in infants, and occasionally in adults, who have cardioesophageal relaxation. The gullet is noted to be patulous in the area where constriction normally should be observed. Ingelfinger[20,35] suggests that this may be a disorder of the vestibule, which is open rather than being closed. Thus, no barrier to gastroesophageal reflux is present.

The term "dyschalasia" has been proposed by Moersch and collaborators[48] to describe a group of patients who have the clinical and roentgenologic characteristics of both achalasia and diffuse spasm, but in whom studies of esophageal motility are not entirely characteristic. The pattern may resemble that of achalasia, with the superimposed pattern of diffuse spasm. The response to cholinergic agents may be equivocal, particularly in the area just above the cardia.

FIG. 7



Intraluminal pressure tracing from an 80 year old man with a small sliding hiatal hernia. The high pressure zone extended from 41 to 39 cm. from the incisors. A dry swallow is shown at the arrow with normal relaxation and then a slow contraction of the intrinsic lower esophageal sphincter which can be seen from the respiratory variations. All three catheters are within the thorax. The high pressure zone was continuous with the hiatal hernia in this patient but the characteristic response to swallowing was noted only at 39 cm. from the incisors. Paper speed was 2.5 mm. per second.

Some patients presenting some of these features appear to have difficulty in conducting the primary peristaltic wave from the transition between striated and smooth muscle of the esophagus.[15] No increased sensitivity to cholinergic agents has been observed in these patients. Further studies will be necessary to determine whether dyschalasia represents a distinct entity or is merely a variant of other conditions characterized by abnormal esophageal motor activity.

The primary deglutition complex may be interrupted at the level of esophageal cancer or at the level of an esophageal ulcer. The complex disappears at the level of the lesion and reappears below this level. Abnormalities in the deglutition pressure gradient have also been observed in patients having functional esophageal distress characterized by dysphagia.[26,49]

The high pressures developed in the distal esophagus explain why rupture of the esophagus occurs almost exclusively in this area. In the act of vomiting, tremendous intra-abdominal pressures develop which may exceed intrathoracic pressures by more than 100 mm. of Hg. These pressures are the result of the downward thrust of the diaphragm and the contraction of the muscles of the abdominal wall. The unusually great intraluminal pressure which is transmitted to the esophagus results in rupture of the esophagus at an area which has been demonstrated to be the weakest part in the esophageal wall.[50]

Reflex disturbances in motor function of the esophagus may occur as a result of primary disease of the gastrointestinal tract elsewhere. We have observed a high incidence of nonperistaltic repetitive activity involving the lower esophagus in patients with active gastric or duodenal ulcer. This pattern returns to normal as the ulcer becomes quiescent.

Discussion

The esophageal phase of swallowing is a highly coordinated act initiated by the pharyngeal constrictors. Normal intra-esophageal pressure is subatmospheric. The esophagus is bounded at either end by a high pressure zone. Both of these zones respond reflexly in

response to the swallowing act. Normal deglutition depends upon coordinated motor activity of the two sphincteric zones accompanied by propulsive activity of the intervening esophagus. If propulsive activity is incoordinated, as in achalasia or scleroderma, swallowing is initiated normally through the first and second stages. The primary peristaltic wave is propagated into the esophagus but disappears shortly below the level of the pharyngoesophageal constrictor. The esophageal phase of swallowing in these patients depends primarily upon the effects of gravity and the pressures generated in the buccal-pharyngeal phase of swallowing.

Normal esophageal transport may also be interrupted by incoordinated motor activity of the lower esophagus, as in patients with diffuse spasm and hiatal hernia. The term "diffuse spasm," although commonly employed, represents a misnomer inasmuch as the manometric observations, indicate that the spasm is usually segmental rather than diffuse. The nonperistaltic waves frequently have an amplitude two to three times that of the normal deglutition complex.

Much attention has been paid recently to the nature of the lower esophageal sphincter. Studies in normal subjects have demonstrated without doubt that there is a physiologic sphincter in the zone of the gastroesophageal vestibule. Studies on patients with hiatal hernia indicate that the vestibule corresponds to the high pressure zone which normally includes an area located above and below the diaphragm. In patients with sliding hiatal hernias this segment is moved upwards into the thorax and the sequence of events of vestibular function can be studied by simultaneous intraluminal pressure measurement and fluorocinematography. These studies appear to indicate that sphincteric activity is a result of coordinated motor activity involving the entire gastroesophageal vestibule and not merely the inferior esophageal sphincter or the constrictor cardiae, as might be inferred from Lerche's concept.

The function of the vestibule during swallowing appears to be that of delaying the passage of swallowed material until the head of pressure is sufficiently great to prevent reflux. The vestibule relaxes and the swallowed bolus enters the stomach. The inferior esophageal sphincter, including the entire vestibular segment, is contracted during the resting state and serves to prevent reflux from the stomach into the esophagus in spite of the positive peritoneal-pleural pressure gradient. The pressures in this segment are such that during each phase of respiration the entire zone, or part of it, acts as a barrier against gastroesophageal reflux. At the end of inspiration only the infradiaphragmatic portion of the physiologic sphincter acts against reflux. At the end of expiration the whole physiologic sphincter fulfills this function. These observations suggest that the infradiaphragmatic portion of the physiologic sphincter is the most important one, since it is the only one that prevents reflux at the moment that regurgitation is most strongly favored by the high pressure difference between the abdomen and thorax.

The normal anatomic relationship between the diaphragm, supporting structures, and the esophagus appears to be important for proper functioning of the intrinsic closing mechanism, a relationship which is lost in patients with sliding hiatal hernia. In these patients the infradiaphragmatic portion of the intrinsic sphincter of the esophagus is located in the thorax where it is subjected to the negative intrathoracic pressures.

Abnormalities of behavior of the lower esophageal sphincter have been demonstrated in patients with achalasia, diffuse spasm and scleroderma. The high pressure zone in untreated patients with achalasia is higher than normal, although most of the difficulty presented by these patients results from failure of the lower esophageal sphincter to relax in response to swallowing.

Higher than normal pressures in the lower esophageal sphincter have also been recorded in some patients with diffuse spasm. The response of this zone to swallowing is erratic and the vestibule may not relax despite repeated attempts at swallowing. The high pressure zone may also extend over a longer distance in patients with diffuse spasm.

The high pressure zone corresponding to the physiologic sphincter at the gastroesophageal junction is greatly decreased or absent in patients with scleroderma. This favors reflux of gastric contents into the esophagus despite the normal anatomic relationship between the diaphragm and esophagus.

The exact relationship of pressure alterations to the symptomatology of patients with esophageal disorders has not been entirely delineated. Some abnormality of the normal pressure gradient of deglutition appears to be present in all patients with dysphagia. If this abnormality of the pressure gradient of deglutition is coupled with failure of relaxation of the inferior esophageal sphincteric segment, as in achalasia or diffuse spasm, dysphagia is even more manifest.

There is substantial evidence that esophageal pain is the result of distention of the esophagus, based upon distention of the esophagus balloon in experimental studies, or in clinical situations as the result of some obstruction to esophageal transport.[51] Although heartburn has been correlated with esophageal reflux,[52] and heartburn can be reproduced by installation of hydrochloric acid into the esophagus,[53] there is evidence that heartburn occurs in clinical situations where gastric acidity levels are low.[51] Jones[54] has indicated that motor disturbances of the esophagus form the basis of the majority of symptoms arising from this organ, and the recent studies tend to support this point of view.

Summary

1. The dynamics of normal deglutition have been described as studied by intraluminal pressure measurements and fluorocinematography.

2. The alterations in esophageal function in patients with achalasia and diffuse spasm, scleroderma, and hiatal hernia have been discussed.

3. Current concepts of the closing mechanism of the esophagus have been discussed.

4. The relationship between alterations in esophageal motility and esophageal symptoms has been briefly reviewed.

Acknowledgments

The authors are indebted to Dr. Craig W. Borden, Chief of Medicine, Veterans Administration Research Hospital, Chicago, and to his staff for cooperation in this work. We would like to acknowledge the valuable assistance of former and current Fellows including Drs. Martin D. Liemer, Ernesto Puletti, and Harold Lazar. Technical assistance was rendered by Junko Mazuta. The illustrations were prepared by Stuart Danovitch who also assisted in the studies.

The fluorocinematographic unit (GE TV-X) was provided by the X-ray Department of the General Electric Company, Milwaukee, Wis. We would like to acknowledge the invaluable technical assistance provided by John E. Jacobs, Ph.D., manager of the Advanced Engineering Laboratory, and of Norman Porath of the General Electric Company.

The list of references will appear with the authors' reprints.

Osteochondritic Changes in the Head of the Femur after Reduction of Congenital Dislocation of the Hip*

J. HIRAM KITE, M.D., *Atlanta, Ga.*

The author is searching for the cause of osteochondritis or aseptic necrosis of the femoral head following the reduction of congenital dislocation of the hip, and questions the necessity for prolonged traction before reduction.

In a study of the late results following closed reduction of congenital dislocation of the hip, it was found that some of the poor results were due to osteochondritic changes in the heads of the femur. Many other factors play a part in producing unfavorable results, such as the age of the patient, the type of dislocation, and the amount of anteversion. This paper, however, will be limited to the study of the osteochondritic changes in the femoral head.

This study is important because of our desire to give our patients the best possible hips, and at the same time not to put the parents to unnecessary hospital expense. The question I am trying to answer, is whether it is necessary to put the child with a dislocated hip in traction for a month before attempting reduction. This long period of traction can be easily carried out in a charity hospital, but this becomes very expensive for the private patient. The cost is most important to young parents who are just above the financial limits of the charity hospital.

Etiologic and Anatomic Considerations

The etiology of osteochondritis has not been definitely established. The degeneration of the capital femoral epiphysis may be due to several factors. The cause most generally accepted is the trauma to the head during reduction, and the pressure of the head against the acetabulum following reduction. For this reason we are told that no hip should be reduced after the age of 6 or 8 months without the use of skeletal traction for 3 or 4 weeks. We are told that the head should be pulled down well below the acetabulum, and held there long enough so that there will be no pressure from tight muscles after reduction.

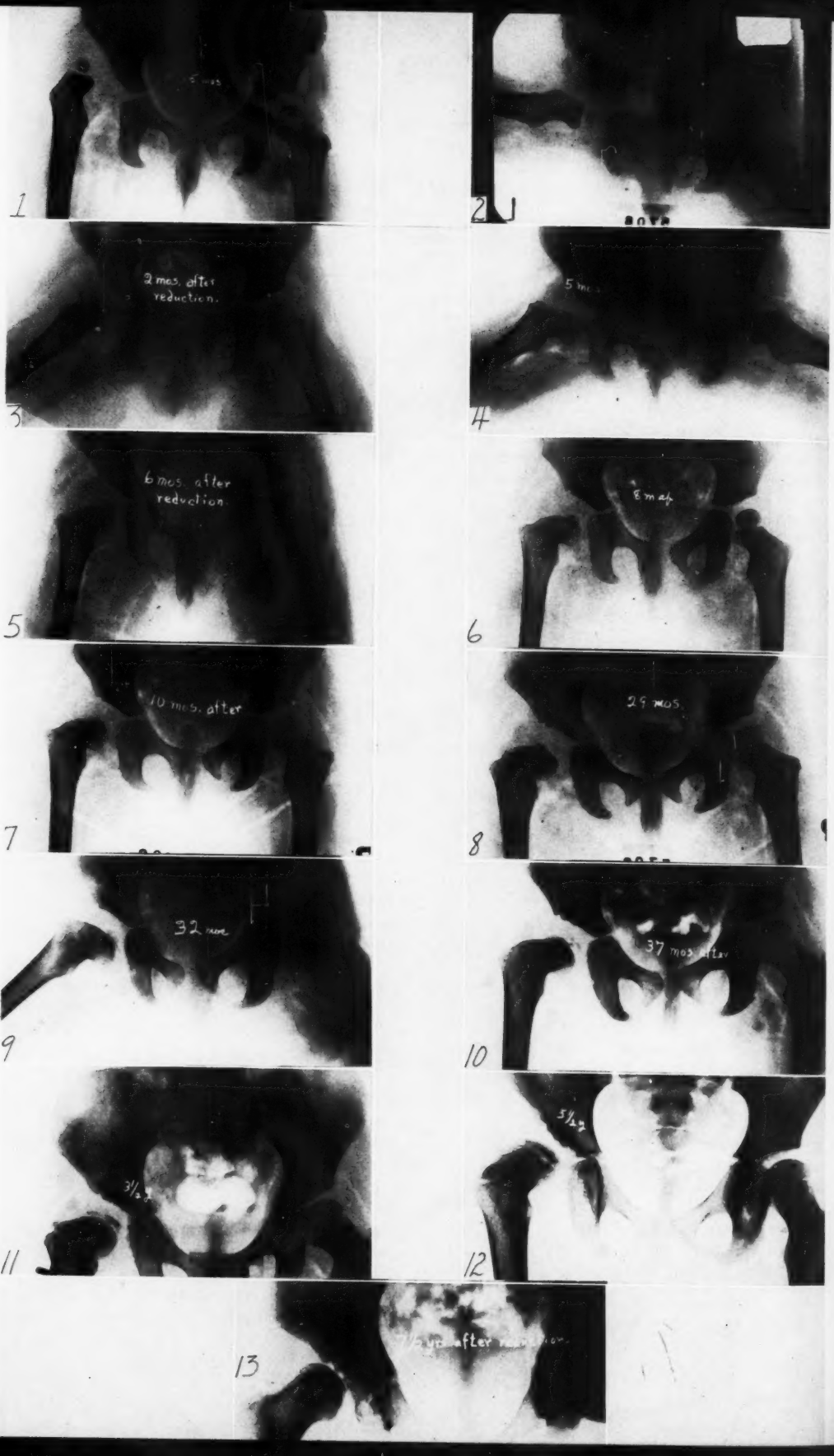
The answer to this problem cannot be found by reviewing the literature. Different authors report the occurrence of osteochondritis from 1% to 50 per cent. For this reason I have made a very careful review of the patients I have treated personally in an attempt to draw what conclusions I could from these patients. An exhaustive review of the literature has been given by Hass.[1]

No standard has been given as to how much change must occur in the femoral head before it can be called osteochondritis, and before it is of clinical significance. A slight irregularity of the head in one x-ray examination is not significant. The alterations must run through a series of x-ray studies.

The time of the appearance of the nucleus for the femoral head varies a great deal in both the unreduced and the reduced hips. In 12 patients in this series in which the head was absent at the time of reduction, the delay in the appearance of the head was from 19 to 39 months after the reduction, with an average of 28 months. In some of these the heads developed from several small centers. These cases should not be confused with those in which there was a well-formed head at the time of reduction.

In this study, only those cases in which there was a well-formed head before reduction, which degenerated and later regenerated, have the terms "osteochondritis" or "aseptic necrosis" been applied. The failure to observe

*Read before the Section on Orthopedic and Traumatic Surgery, Southern Medical Association, Fifty-Second Annual Meeting, New Orleans, La., November 3-6, 1958.


1
2
2 mos. after reduction.
3
4
6 mos. after reduction
5
8 mos.
6
10 mos. after
7
29 mos.
8
32 mos
9
37 mos. after
10
11
12
13

this point has added error to some of the previous reports (Fig. 1).

In a typical case, the first change noticed in the nucleus for the head is when the x-ray examinations are made when the spica is changed for the first time after reduction, which is usually between 4 and 8 weeks after reduction. At this time it is noticed that the center of ossification for the head has failed to grow. The head also shows a slight atrophy. In the meantime, the head on the normal side has shown a slight increase in size. On the next change of cast the head on the dislocated side will still be the same size it was before

FIG. 1

1. *Fifteen month old girl with unilateral congenital dislocation of hip.*
2. *Immediately after reduction, under ether anesthesia, the hip slipped in place very easily. The hip was flexed and light traction made upward on the leg and the leg abducted and the hip slipped in on the first movement and without force. The hip was not allowed to dislocate and a spica applied.*
3. *Two months after reduction there has been no growth in the dislocated head while the normal head shows a slight increase in size.*
4. *Five months after reduction there is still no increase in the size of the head. Normal epiphyseal line is evident in the lateral view.*
5. *Six months after reduction the head is smaller and appears to have sunk down into the metaphysis of the neck.*
6. *Eight months after reduction the head is still smaller and shows areas of lessened density.*
7. *At 10 months the head is shown to be almost absorbed into the neck with no growth of either the head or neck.*
8. *Twenty-nine months after reduction the head can scarcely be seen.*
9. *At 32 months the head is stationary.*
10. *At 37 months the head has almost completely disappeared but is well placed in the acetabulum.*
11. *At 3½ years the head is reforming from several centers of ossification.*
12. *At 5½ years the head has reformed but is thinner than the normal head and still shows radiolucent areas.*
13. *Seven and one-half years after reduction the head shows almost normal density. The leg is 2.2 cm. shorter than the opposite leg and motion is limited to about half the normal range.*

reduction. It will show more atrophy and may begin to show cystic changes. The x-ray studies 5 to 7 months after reduction will show an irregularity of the head. The head may show very faintly at this time.

In the anteroposterior view, the nucleus for the head appears to have sunk down into the metaphysis of the neck by about the sixth month. The epiphyseal line at times cannot be seen in this view. In the lateral view the head can be seen more distinctly, and the epiphyseal line is visible. Sometimes the head remains as a very faint flat shadow, or it may completely disappear and not reappear for some months.

When the head does begin to regenerate, calcium may be deposited in one or more irregular masses, very much like the regeneration of the head in Legg-Perthe's disease. When the head reforms early, a more nearly normal head forms. When there is a long delay in the reappearance of the head, the final head is more irregular in shape. Sometimes it enlarges and becomes mushroom in shape and more than fills the acetabulum. In all of these cases the metaphysis of the neck is affected as well as the epiphysis for the head. It seems that there is an injury to the epiphyseal line and that growth is delayed on both sides of it. A short neck may develop in these cases, and in a few a coxa vara develops. When followed into adult life some of these patients show almost no neck.

Clinical Study

A study of all instances of congenital dislocation of the hip in one large group leads to much confusion. Most of the cases fall into one large group which we may call "typical." Those which fall into the "atypical" group have been subdivided in this study into four groups.

(1) *Arthrogryposis multiplex congenita.* I reported 54 patients with arthrogryposis in 1954.[2] Twenty-three of these had congenital dislocation of the hips, and in 12 the dislocation was bilateral. Many of these hips presented a deep false acetabulum at birth, or developed a deep acetabulum during the first 6 months. Attempts were made to reduce the hips in 12 of these patients. In only 5 could the hips be reduced, and only one of these gave a really good result. These children with arthrogryposis and a deep false acetabulum have a better result when left alone.

(2) *Spina bifida.* It is felt that these cases should be placed in a group to themselves since they behave differently. Because of the paralysis, the hip can often be slipped in without an anesthetic, but when the spica is removed the hip slips out easily. There are no normal muscles to hold the hip in place. There were 18 patients in this group.

(3) *Defective group.* In this group were placed the children with gross defects of the femur and of the lumbar spine and sacrum. No attempt was made to reduce any of these. There were 7 cases in this group.

(4) *Congenital absence of head and neck of*

femur. I have not seen this group mentioned in the literature. There were 7 cases in which no head ever formed, even when followed into adult life. When reduced the short neck remained in the acetabulum and formed a neoarthrosis.

Two hundred and two cases of congenital dislocation of the hip were available for study at the Scottish Rite Hospital for Crippled Children. (This was through 1955.) In addition to the above, 21 cases were eliminated because the follow-up was less than two years. Twenty-nine cases were too old for treatment when they were brought for examination. This left 97 "typical" cases for study. All of the reductions were done by me or in my presence. There was only one open reduction in this series. After reduction in the earlier days, the hips were placed in a spica in a "ninety-ninety" or frog position. In more recent years, the hips were abducted only 60 to 70°, and were flexed from the table level about 15 degrees. All have been placed in neutral rotation, so that the flexed knee pointed toward the floor. If the head could be easily reduced after the patient was well relaxed by the anesthetic, it was reduced. If the reduction was difficult traction was used. In the early days much force was used in the reductions, but in the later years the attempts at reduction have been gentle. Traction apparatus is always available before attempting the reduction.

To make a more accurate study of these cases, they were placed in age groups, and then each age group subdivided as to whether or not traction was used before reduction. The results are shown in table 1. There were 65 cases reduced without traction. Eleven, or 17%, developed osteochondritis. Thirty-two were reduced after traction and 7, or 22%, developed osteochondritis. To summarize: of 97 "typical" cases, 18 patients or 19% developed aseptic necrosis of the head. According to Hass', Lange reported this change in the head in 20% of his cases, and so did Brandes and Hilgenreiner in 17.8% of 157 cases.

Causes of Osteochondritis

There are three chief causes, two of which are generally accepted, and the third which I am suggesting as possibly the more important cause.

(1) *Trauma*. We have been told by many writers in the past that it was the trauma of reduction which caused this change in the head. Some have wondered if the examination by the pediatricians and house doctors shortly after birth, to demonstrate Ortolani's jerk might not injure the cartilagenous head. Others have insisted that all babies over 6 or 8 months of age should never be reduced without bringing the hips out in abduction on a frame, or by the use of skeletal traction. Some have recommended that this traction be maintained for at least 4 weeks; that it be strenuous enough to pull the head well down below the rim of the acetabulum and that the traction should be continued until the head slips in spontaneously, or until the head goes in by simply lifting up on the end of the femur.

(2) *Pressure*. Those who insist on preliminary traction, say that it is the pressure of the head against the acetabulum which causes the melting away of the head; that when the head is reduced without traction, the adductor muscles become tight and crowd the head against the acetabulum; that this is made worse when the legs are abducted to the so-called frog or "ninety-ninety" position.

(3) *Atrophy*. It is my belief that atrophy from the immobilization in spicas is the most likely cause of this osteochondritis.

Discussion of these causes. Cases encountered in this study offer some facts for consideration. The 29 patients who were too old for reduction cover a range up to 20 years. These

TABLE 1

		Number of Patients	*Number Developing Osteochondritis*
Under one year	No traction	11	1
	Traction	6	0
Between 1 and 2 yrs.	No traction	38	9
	Traction	1	0
Between 2 and 3 yrs.	No traction	11	0
	Traction	10	3
Between 3 and 4 yrs.	No traction	2	0
	Traction	6	0
Between 4 and 5 yrs.	No traction	1	0
	Traction	2	2
Over five years	No traction	2	1
	Traction	7	2
		97	18

Sixty-five cases were reduced without traction. Eleven, or 17% developed osteochondritis. Thirty-two cases were reduced after traction and 7, or 22% developed osteochondritis of the femoral head. In this series traction did not lessen the occurrence of osteochondritis, but it was used only in the more difficult cases.

all show smaller heads than normal and somewhat shorter necks. None showed any osteochondritis. These heads were not subject to trauma, pressure or atrophy from immobilization.

In studying the effects of *trauma* the following cases should be considered.

Case. A 4 year old girl was treated for unilateral dislocation of the hip. Between 1924 and 1926 she was given six anesthetics and three different orthopedic surgeons each tried twice to reduce this hip. A great deal of force was used for over an hour on some of the last attempts before giving up. This hip was never reduced. Its course was followed for 7 years with x-ray studies and it never showed any sign of osteochondritis. It had trauma, but no pressure on the head and no atrophy from immobilization.

Case. A 2 year old girl had a bilateral dislocation. The hips were easily reduced without the use of traction. The spica was removed at 7 months. By 10 months the right hip had slipped out. She was given a second anesthetic, and this hip was again subjected to the trauma of a second reduction. This hip developed normally, while the hip which had the trauma of only one reduction developed osteochondritis.

Case. A 4 year old girl with bilateral dislocation of hips had 2 weeks traction and an attempt at reduction of the hips in 1930. The right hip was reduced, but after much manipulation the left hip could not be reduced. A double spica was applied and in 2 weeks a second attempt was made to reduce the hip, which was unsuccessful. The spica was reapplied with the leg abducted. Two weeks later she was given a third anesthetic. When the usual manipulations were unsuccessful she was turned on her abdomen, and the left hip forced into the acetabulum with pressure over the greater trochanter after the method of Davis. Much force was used. Both hips retained their reduction. The right which went in easily developed osteochondritis, and still showed a somewhat flattened head 13 years later, while the left hip which had the trauma for three manipulations developed no osteochondritis.

Case. A 23 month old boy with bilateral dislocations showed no shadows for the heads. Both hips were reduced easily without traction. After the removal of the spicas the left slipped out. He was anesthetized and the hip reduced. It slipped out again after removal of the spicas. He was given a third anesthetic and the hip was again reduced. A short time later the hip slipped out the third time, and again it was reduced with more difficulty. After the trauma of four reductions, this left hip stayed in. He is now 7 years old and has well formed heads on both sides, and both look alike.

I know that it is not safe to draw conclusions from a few cases, but these suggest to me that trauma might not be the sole cause of osteochondritis.

The effect of *pressure* on the femoral head.

Case. A 19 month old girl with bilateral dislocations had heads which were the same size in the x-rays and which looked alike before reduction. Both hips were reduced easily without preliminary traction. Both were placed in the same amount of abduction in a double spica, and both were maintained the same time. When the spica was removed both were subjected to the same strain from weight-bearing. One hip developed osteochondritis and the other developed normally. Twenty-four years after reduction the one with osteochondritis has limitation of motion, some pain, and a very short neck as shown by x-ray examination.

Case. A still more interesting case was a 2 year old girl with bilateral dislocation of the hips. The heads were present and the same size and the position of each hip was the same before reduction. When she was brought to the operating room, having been given the usual preliminary drugs before anesthesia, we again examined the hips. To our surprise one hip slipped in when we lifted up on the thigh. This was tried on the other hip and it also slipped in easily. No traction had been used. A double spica was applied without letting the head slip out. Spicas were worn for 7 months. One of the heads developed normally, and the other developed osteochondritis. Her course has been followed with yearly x-ray studies for 10 years. The head which developed osteochondritis shows an irregularly shaped head and short neck, and some limitation of motion on that side. It is hard to believe that the reduction without preliminary traction is responsible for the osteochondritis in this case. The hip was subjected to pressure and atrophy.

When the head is reduced with or without traction, some tension is placed on the muscles by slightly increasing the length of the leg by putting the head in the acetabulum, and by abducting the leg. In all of the older children in this series tension was partly relieved by an adductor tenotomy. In the last 15 or 20 years the pressure has been lessened by having the leg in neutral rotation and slightly flexed and abducted not more than 60 to 70 degrees. Even when this is done, it is hard to believe that much sustained pressure is placed on the head. The muscles are elastic and stretch easily. When the head is reduced and allowed to slip out and is immediately reduced again, it goes in more easily after the first stretching of the muscles. We know that the muscles are easily stretched, because traction will pull the head down from 2 to 4 cm. There is probably no prolonged pressure on the head after reduction.

Atrophy. This is probably the most important factor in the production of osteochondritis. Perhaps it is not the pressure of the head of the femur against the acetabulum that causes osteochondritis, but the reverse, the lack of pressure. With complete immobilization in the double spica the muscles soon atrophy.

It has been shown that the stress stimulus is the most important factor in the stimulation of bone growth.[3] Throughout the skeleton mechanical stress is apparently necessary to convert primitive bone into the adult type of bone.

The lack of stress can be dramatically illustrated by comparing the x-ray films of a fracture made at the time of the fracture with those made when the cast is removed. Even 5 or 6 weeks may show severe deossification of the bones. In the treatment of clubfeet, after long immobilization in casts, we frequently see cystic changes in the bones. The treatment of no other condition requires such long immobilization as that for congenital dislocation of the hip.

We have in the dislocated hip a defective "anlage." In the head there is an inhibition of transformation of primordial cartilage into bone. This inhibition affects not only the epiphysis for the head, but the neck, the ilium and the entire side of the pelvis. The ischiopubic synostosis shows a wider opening on the side of the dislocation, and there is considerable delay in the closure of this space. Might not this premature head be more vulnerable to the effects of disuse atrophy?

Other factors which might produce osteochondritis. Axhausen thought that aseptic necrosis of the head was due to bland mycotic embolism in the distribution of the afferent vessels. Many have claimed that the pressure of the head against the ligamentum teres interfered with the blood supply to the head. Trueta[4] has shown recently that very little blood reaches the head through the ligamentum teres during the first few years of life.

The factors causing the change in the head of the femur after reduction of the hip are probably different from those producing the osteochondrosis we see in Kohler's disease, Osgood-Schlatter disease or Legg-Calve-Perthe's disease. These come on without gross trauma, pressure, or immobilization.

The changes in the head after reduction has been compared to Perthe's disease because the appearance of the regeneration of the head as shown by the x-ray examination is somewhat similar. However, these are two very distinct conditions. The changes in the head of the dislocated hips come on very shortly after reduction, regardless of the age of the patient. Ten of the 18 cases occurred before the age of two. Perthe's appears between 4 and 8 years, with most cases occurring at six. The sex distribution is not that of Perthe's disease. In Perthe's disease in our series 86% were boys.[5] In these 202 dislocated hips 75% were girls. In the 18 children showing osteochondritis, 13 or 72% were girls. The sex distribution is that of the hips themselves.

It is interesting to observe that 2 boys in this series, while resting in bed in a unilateral spica, developed aseptic necrosis in the normal hip. This was thought at first to be a part of the change which was occurring in the dislocated hip, but one of these boys was 5, and old enough to develop typical Perthe's disease. The osteochondritis in the normal hip might have been caused by disuse atrophy.

As mentioned above, in the early days a great deal of force was used in reducing the hips as was the custom 30 years ago, and still 80% of the cases showed no trace of osteochondritis.

The orthopedists who insist on skeletal traction in all patients over a year old, can say that the traction used in my cases was not adequate and that it was not used long enough. This perhaps is true for some of the earlier cases, but the x-ray studies in the later cases show that the head was pulled down well below the acetabulum. Most of the patients were held in traction for from 3 to 5 weeks. Since the percentage of osteochondritis in this series was the same in those cases in which traction was used as it was in those in which it was not used, I can only say that it did not prevent osteochondritis in my cases.

I am not opposed to traction. It does make the reduction easier, and it should be used in all cases where the reduction is difficult. However, I do not believe that a child should be subjected to the position necessary for traction, and the family of the private patient be inconvenienced by wanting to stay with the baby for a month in the hospital. Neither do I believe that the family should be put to this extra expense nor a hospital bed be tied up for a month, just to follow an established routine.

Results in the cases of osteochondritis. The follow-up time on these 18 patients was from 2 to 24 years, with an average of seven and a half years. Eleven patients developed a thin

head with a smooth outline, giving a fair functional result. Five presented a rather severe coxa vara. Two developed a mushroom shaped head too large for the acetabulum. When followed into adult life they all had very short necks. In one the head disappeared completely and had not reappeared 4 years after reduction.

Summary

One of the causes of the poor results after reduction of congenital dislocation of the hip is the osteochondritic changes which occur in the head. Two hundred and two patients with congenital dislocation of the hips have been reviewed. It has been thought that the osteochondritis was due to the trauma of reduction and the pressure of the head against the acetabulum. For this reason it is argued that prolonged traction should be used in all cases before reduction. This is easy for charity patients, but expensive for private patients. Nineteen per cent of my patients showed osteochondritis after reduction. This occurred as frequently in those patients who had traction as in those in whom reduction was without traction. The osteochondritis is probably due to the atrophy following the long immobilization in casts. If this is true, it is permissible to reduce the hips which can be reduced easily, without traction. Traction will make the reduction easier for those difficult to reduce.

References

1. Hass, Julius: Congenital Dislocation of the Hip. Springfield, Ill., Charles C. Thomas, Publisher, 1951.
2. Kite, J. H.: Arthrogryposis Multiplex Congenita. Review of Fifty-Four Cases, South. M. J. 48:1141, 1954.
3. Aegerter, E., and Kirkpatrick, J. A.: Orthopedic Diseases. Physiology, Pathology, Radiology. Philadelphia, W. B. Saunders Co., 1958, p. 40.
4. Trueta, J.: The Normal Vascular Anatomy of the Human Femoral Head During Growth, J. Bone and Joint Surg. 39-B:358, 1957.
5. Kite, J. H., and French, G. O.: The Early Diagnosis of Flat-headed Femur, South. M. J. 45:581, 1952.

ARE YOU MOVING?

Please send the following to: Southern Medical Association

2601 Highland Avenue, Birmingham 5, Alabama

Name.....
(Please print)

Old Address:

Street.....

City and Zone.....

State.....

New Address:

Street.....

City and Zone.....

State.....

The Hazards of Radium Accidents*

H. STEPHEN WEENS, M.D., and R. H. ROHRER, Ph.D.,† *Atlanta, Ga.*

All those dealing with radioactive materials are much more aware of the potential hazards at the present time than in past decades. It is probable that most contamination by radium usually went unnoticed in the past.

THE HAZARDS OF FAILURE of encapsulated radium sources are often not fully appreciated by those handling radium in clinical practice and laboratories. The use of artificial radioactive isotopes is controlled by detailed requirements of the Atomic Energy Commission, but the employment of radium sources in hospitals, physicians' offices and laboratories is not covered by explicit recommendations except for those contained in handbook No. 54 of the National Bureau of Standards.[1] Unfortunately, these recommendations are often not known to those who are involved in the handling of radium sources in institutions.

It should be realized that the radiation hazards incident to the leakage or spillage of radium salts are considerable inasmuch as radium has a long half life, is an alpha emitter, is slowly excreted by the body, and is a selective bone seeker. It represents, for these reasons, a much greater radiation hazard than such artificial radioactive isotopes as I^{131}, Co^{60} and Au^{198} which are introduced in clinical practice.

The dangers of absorption of radium by ingestion or inhalation are well known from observations of chronic radium intoxication in industry.[2] Briefly, the principal pathologic changes incident to radium poisoning are damage and necrosis of bone, development of bone tumors and blood dyscrasias. More precise information concerning radium metabolism has been obtained by recent studies of the Biological and Medical Divisions of the Argonne National Laboratory.[3] Workers in that laboratory had the opportunity to study a fairly large number of individuals who had received known amounts of soluble radium salts parenterally and orally for therapeutic purposes. It has been shown that radium may be retained tenaciously in the bone over prolonged periods of time. After a lapse of several months from 5 to 15% of the injected soluble compounds were retained in the body. After approximately 20 years 0.6% was still retained in the human body, largely in the skeletal system.

The metabolism of insoluble radium salts such as radium sulfate is less well known. Studies by Marinelli and associates[4] indicate the metabolism of insoluble radium salts is somewhat different from soluble compounds. There is prolonged retention of the radium salts in the lung where the particles may be phagocytosed and transported to other parts of the human body. More information as to the fate of insoluble radium salts in the human body appears highly desirable inasmuch as many recent radium accidents were concerned largely with absorption of these compounds.

The maximum permissible body burden for radium fixed in the body is given at 0.1 micrograms.[5] It is noteworthy that individuals who had retained this amount of acceptable body burden after absorption of radium many years before are known to have developed minor bone changes. Bone sarcoma is known to have developed in individuals in whom the body burden was as little as 0.5 mcg. remaining in the body from the administration of radium many years in the past.

Though the clinical application of radium sources is sufficiently well described in many books of radiotherapy, it is surprising that little attention has been paid in these texts to the actual hazards incident to the handling of radium sources once leakage or breakage should develop. Unfortunately, only a small number of papers have appeared in the literature emphasizing those methods which are essential in the prevention of accidents or

*Read before the Section on Radiology, Southern Medical Association, Fifty-Second Annual Meeting, New Orleans, La., November 3-6, 1958.

†From the Grady Memorial Hospital, Atlanta, Ga.

demonstrating those procedures which should be immediately selected once such an accident might have occurred.

Recent experience in a radium accident in one of our associated hospitals has stimulated us to review briefly some of the problems arising from such an event. It is hoped that such a discussion may be of practical value to others involved in the clinical application of radium. In this manner radium accidents may be prevented or minimized, and intelligent management of spillage or leakage may eliminate hazards to the human body and avoid severe financial losses.

Dangers Associated with Containers

Radium containers generally available consist of platinum-iridium cells, needles, tubes, and capsules. Cells and small needles are directly loaded with a radium compound. Catalogues and certificates of many radium suppliers do not specify the chemical form of the radium compound. The very slightly soluble radium sulfate is often used, but there are reports that the radium chloride is sometimes employed, and this is an extremely soluble salt. Large needles, tubes and capsules may contain one or more sealed cells or may be loaded directly. The caps may be secured by a press-fit, threaded sockets, or soldered.

Containers loaded directly offer the greatest hazard inasmuch as any small leak due to failure of the wall of the cell will allow the escape of radon emanation or perhaps the radium salt itself. Doubly sealed containers are safer but even these may fail to contain the radium salt if certain circumstances arise.

The failure of a container may be due to several factors. These include mechanical damage to the container due to such accidental misuse, as bending or crushing during handling of the container. Storage boxes and portable lead shielding are most notorious as instruments of destruction.

Thermal damage to the container (overheating) may weaken soldered seals, or may cause a press-fit cap to come loose as a result of unequal expansion of the tube and its cap.

Radiation damage causes metallurgical changes due to high doses. Soldered seals are known to have weakened due to this effect. Press-fit caps may work loose as a result of a break-down of the metallic structure of a container. For this reason old radium cells should be the first to be suspected of offering a potential hazard. Old preparations which may be unsafe are in the possession of physicians in all branches of medicine.

Improper filling technics are another source of trouble. All sealed sources must withstand a certain radon gas pressure. There are cases where the explosion or rupture of capsules is believed to be due to a high internal pressure developed by the decomposition of water present in a radium salt at the time of loading.[6]

If a failure is such that the radium salt escapes from the container, a hazard to the health of personnel will exist. The powdered salt may be carried by air streams or by tracking on shoes to many new locations. The dangers of ingesting the salt have already been mentioned. The problem is not limited to contamination from the radium salt alone. Radium decays to radon gas which may diffuse through the air to many areas in a closed building. The radioactive decay of radon leaves solids which emit alpha-, beta-, and gamma-rays. These solid materials may be deposited on floors, walls or other surfaces of a room or suite of rooms. It is of some significance that almost all of the gamma-rays emitted from a radium container are due to decay products of radon-radium B and radium C. Thus, it is conceivable that if radon gas escapes into a room either by emanating from a radium compound present in the room or by leakage from a radium capsule, radioactive materials may eventually be distributed on all surfaces of the room.

The removal of contamination due to the failure of a radium container should be attempted only by highly trained personnel and is a laborious process. There are reported cases where clean-up procedures have cost hospitals and other institutions several hundreds of thousands of dollars.[7,8]

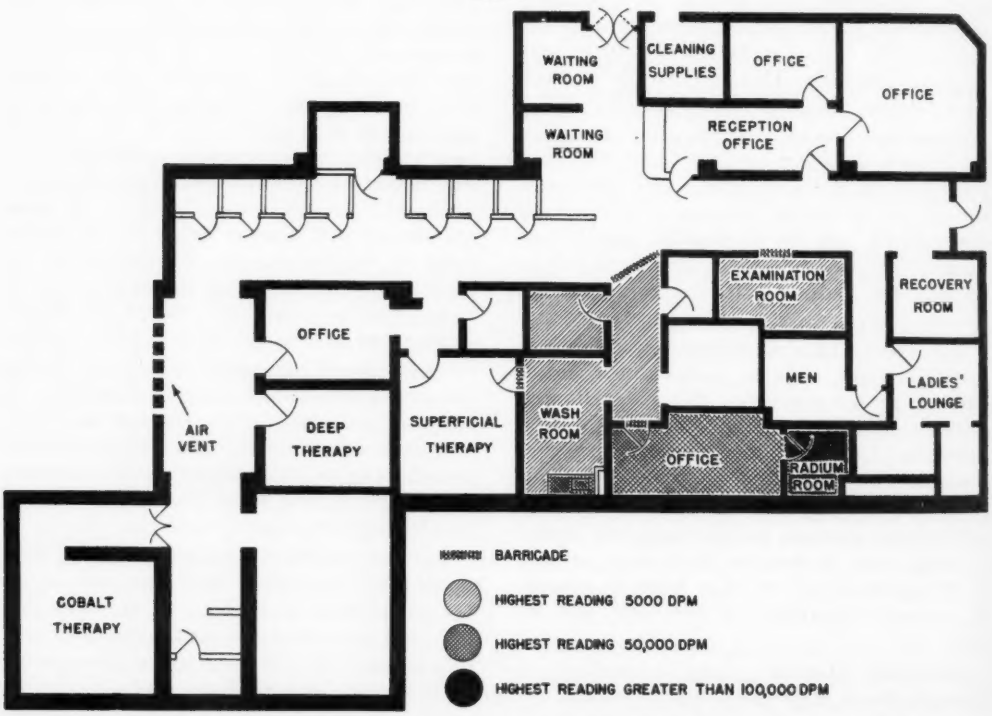
Radium accidents are infrequent but there is always a possibility that one may occur. Questions arise as to how an accident may be avoided or if one should occur what procedure must be followed to avoid exposure of personnel and to keep clean-up cost at a minimum.

Radium Spill

A brief account of an accident which occurred last summer in an Atlanta hospital and the clean-up procedure may be of interest and may serve as an example for discussion. On the afternoon of June 24, 1958, the cap of an encapsulated 25 mg. source of radium became disengaged from the body of the capsule in routine handling. The capsule was loaded directly with radium sulfate as the active compound. The cap was secured by a press-fit, and an eye for sutures was located in the cap. Before the seriousness of the situation was realized, about 2.5 mg. of radium had been lost from this container. Prompt action was then taken. The chief radiologist and the radiologic physicist were notified, the air-conditioning system was cut-off, and the rooms in which the open capsule was handled were locked and persons who handled the source proceeded with washing.

The first survey was done on the same day to determine the extent of the contamination. Unfortunately only Geiger-Mueller and ionization chamber type of survey instruments were available at that time. These proved to be inadequate for several reasons. Radium contamination of a fairly high level at the scene of the accident was not easily detected because of a high background due to radiation from the radium storage safe which was located in the same room. In areas suspected of contamination but remote from the storage safe, these instruments were not sufficiently sensitive to detect objectionable quantities of radium. The initial survey revealed that some spillage had occurred but the extent of the damage was left unevaluated. Through the assistance of the State Public Health Department, contacts were made with the United States Atomic Energy Commission, Lockheed Aircraft Corporation, the United States Public Health Service and the Health Physics Division of the Oak Ridge National Laboratories. These organizations very generously supplied instruments and personnel for a complete survey of the area.

FIG. 1



Floor plan of the radiation therapy section of the hospital. Areas where contamination was wide-spread are indicated by cross-hatching. The spill occurred in the Radium Room.

Survey and Decontamination

A plan of the affected area is shown in figure 1. This area comprises the x-ray and radium therapy section of the hospital. The accident occurred in the radium room and in an adjacent "office." The radiation survey consisted of making direct readings of alpha emitter contamination on the floors, walls, ceiling and furniture, using a large area "Sampson" alpha-ray detector and by indirect readings using a "wipe-test" technic. Numbered filtered paper pads were wiped on areas of from one to four square feet, first monitored by a "Sampson" instrument, then counted on an alpha proportional counter in the State Public Health Department Laboratories. The air contamination was also measured using a large volume air sampler which drew air through a filter which was promptly counted in a proportional counter.

Results of the survey showed that some spots on the floor in the radium room and office had readings of more than 100,000 disintegrations per minute (the limit of measurement of the "Sampson" instrument). This is the equivalent of more than 0.1 of a mcg. of radium per 75 square cm. of floor area. Contamination on the walls was almost nonexistent. (It might be of interest to note that we have obtained alpha activities of 20,000 disintegrations per minute from an unprotected face of an alarm clock, and that in some cases wrist watch dials have been found to contain as much as 2 mcg. of radium.)[9] Traces of alpha activity were found throughout the entire x-ray therapy area. A small "hot-spot" was found on the air-exhaust grill far removed from the scene of the accident.

From the survey it was evident that some radium had been tracked from the scene of the accident on the shoes of the participants. Several pairs of shoes were found to be too radioactive for decontamination and had to be discarded.

Before the decontamination began, the area was secured in the following manner. The ventilators and the doors to the office and radium room were sealed with masking tape to prevent further spread of the radium from that area. Barriers of Kraft paper sealed with masking tape were set up to seal off the moderately contaminated areas shown in figure 1 by 45 degree cross-hatching. The entire therapy section of the hospital was closed and x-ray therapy for the hospital carried on in another section using temporary equipment.

The decontamination was carried out in three phases. The hospital physicist with the help of a local work crew decontaminated the floors and the walls of the area outside of the barriers. This was accomplished by swabbing the contaminated surfaces with ABD pads which were moistened with versene solutions and detergents. Versene is a chemically chelating agent with an affinity for heavy metals. The pads were used only once and were disposed immediately in order to prevent spreading of the contamination. The cleaning crew wore operating room scrub clothes, gauze masks, surgical gloves, and paper shower scuffs which were disposed with other contaminated materials. The contaminated clothes, swabs and other materials were stored at the end of the hallway opposite the recovery room. After it was determined that the decontamination was complete for this outside area, the floors were waxed and the x-ray therapy unit opened for limited occupation of the staff only.

The second phase was the decontamination of the highly affected area consisting of the radium room and the office. This was carried out by a group of health-physics personnel from Lockheed Aircraft Corporation. To avoid danger of contamination from radon and radium sulfate dust, these persons wore complete protective uniforms. Contaminated objects which could not be made safe by washing were sealed in plastic covers and prepared for disposal. The asphalt tile flooring was first vacuum cleaned using a commercial device with a water-trap filter then either washed with versene or acetone, or sprayed with a plastic material and removed.

The third phase consisted of a clean-up by the local crew of the remaining mildly contaminated area. All contaminated materials were eventually sealed in leakproof metal drums for disposal by the Lockheed group. The estimated direct cost of the operation to the hospital was about $3,000, but might have run up to $10,000 if the radiology personnel had not exercised immediate caution upon discovering the loss of the radium from the capsule.

Discussion

The failure of sources of encapsulated radium appears to be quite infrequent; however, there is a great possibility it may go undetected. Discussions with radiologists indicate that it is likely that such incidents occur more commonly than are publicized in the literature. Physicians may not always take precautions to detect leaks in their radium cells because the necessary equipment is not generally present in all hospitals and offices. It is our opinion that annual checks for leaks of radium capsules are not adequate.

As a result of our experience, we are proposing for our departments several changes in our technics of handling radium which we believe might serve as safeguards against some future accidents. We propose a procedure such that tests for leaks can easily be performed with each use of the encapsulated source. To effect this, radium containers not in applicators are stored in glass tubes with rubber stoppers. A piece of absorbent cotton or filter paper is placed inside of the tube. In the event of any leakage, products of radon decay will be deposited on the absorbing material. When the glass tube is removed from the safe it is carried from the radium storage room to a location of lower radiation level in a small shield where it can be checked for activity with a Geiger-Mueller survey meter. Evidence of leakage can be detected by holding the absorbent material close to the Geiger-Mueller tube. For a critical test, the radium sources should be moved far enough from the instrument to permit a sensitive measure of the activity of the cotton.

We have several suggestions concerning the procedure to follow in the event of a suspected spill. Precautions must be taken immediately to prevent the spreading of radium or radium salt. This may require the securing of windows and turning off the air-conditioning equipment connected with this room. It is also important that individuals who handle the radium at the time of the suspected spill leave their shoes and probably contaminated clothing behind at the scene of the spill. As soon as the area has been secured the involved persons should wash and shower well to remove radioactive materials. Persons who have been exposed to radioactive materials should be monitored immediately after washing. We have to emphasize that for this purpose a Geiger-Mueller counter is not adequate. If radium is present on the skin, alpha particle radiation is much stronger than gamma radiation. It is essential that an instrument sensitive to alpha radiation be used to monitor personnel following an accident. If an institution is not equipped and its personnel drilled to handle the situation of a radium spill it should seek the immediate help of some group that is. One should feel free to call upon the nearest inspection office of the Atomic Energy Commission or the Health Physics Division at the Oak Ridge National Laboratory for assistance. We found our own State Public Health Department to be most cooperative in helping us to secure the instruments and consultative services necessary to help us in evaluating our situation. Some industries have health-physics divisions if they are handling radioactive sources, but usually these people are not acquainted with problems of radium contamination. Commercial services are available from several corporations which advertise in the isotope and radiological journals.

We would like to stress that we do not believe one should undertake an evaluation survey himself unless he is adequately equipped with the necessary instruments and has had some experience with a radium spill. Instruments must include alpha radiation detectors equivalent to the "Sampson," or a large area proportional counter which does not respond to gamma rays, filter paper for making wipe tests, an air sampler to determine the dust content and radon content of the air, adequate protective clothing, including dust masks, rolls of paper or plastic to spread over floors on the very first advance into the contaminated area, and masking tape for sealing doors to contaminated areas. Hesitancy to call in experienced personnel may result in spreading contamination to areas adjacent to the spill and might, in the long run, cause the cost of the eventual decontamination of the building to run into astronomical figures. Finally, we would stress the suggestion that everyone who handles radium whether they be doctor, nurse, technician, or machinist should know what immediate steps should be taken in the event of a radium accident.

References

1. Protection Against Radiations from Radium, Cobalt^{60}, and Cesium^{137}, National Bureau of Standards Handbook 54:31-36, 1954.
2. Evans, R. D.: Protection of Radium Dial Workers and Radiologists from Injury by Radium, J. Indust. Hyg. & Toxicol. 25:253, 1943.
3. Looney, W. B., Hasterlik, R. J., Brues, A. M., and Skirmont, E.: A Clinical Investigation of the Chronic Effects of Radium Salts Administered Therapeutically (1915-1931), Am. J. Roentgenol. 73:1006, 1955.
4. Marinelli, L. D., Norris, W. P., Gustafson, P. F., and Speckman, T. W.: Transport of Radium Sulfate from the Lung and its Elimination from the Human Body Following Single Accidental Exposures, Radiology 61:903, 1953.
5. Maximum Permissible Amounts of Radioisotopes in the Human Body and Maximum Permissible Concentrations in Air and Water, National Bureau of Standards Handbook 52:14, 1953.
6. Cross, F. H., Miller, H., and Mussell, L. E.: An Unusual Radium Accident, Brit. J. Radiol. 24:122, 1951.
7. Gallaghar, R. G., and Saenger, E. L.: Radium Capsules and Their Associated Hazards, Am. J. Roentgenol. 77:511, 1957.
8. Skow, R. K., Vandivert, V. V., and Holden, F. R.: Hazard Evaluation and Control After Spill of 40 mg. of Radium, Nucleonics 11:45, 1953.
9. Haybittle, J. L.: Radiation Hazard from Luminous Watches, Nature 181:1422, 1958.

Fifty-third Annual Meeting of Southern Medical Association in Atlanta, Ga., November 16-19, 1959

Medicolegal Aspects of Anesthesiology*

A. J. OCHSNER, II, M.D., *Alexandria, La.*

In spite of the title, it would be well for every physician to review the medicolegal aspects of medical practice irrespective of the field. All this is well summarized here.

IN THE RECENT COURSE of the practice of medicine, the legal aspects have crept more and more into the picture. Suits against physicians have become frequent, rather than rare. These suits for alleged malpractice, or assault, may or may not have merit, as may be determined by judge or jury. These cases are a nuisance and a menace to the physician, and they are costly. Any physician may be sued by a patient, and the anesthesiologist is no exception. This aspect of medicolegal problems forms the basis of this paper.

The rule of law is that the operating surgeon is responsible for, and accountable for the actions of personnel in his operating room.[1] This principle also applies to a nurse-anesthetist who may be used by the surgeon. This is not the fact when a physician, or a physician-anesthetist, is administering the anesthetic. "A surgeon is not ordinarily liable for the negligence of his physician-anesthetist, provided the latter is qualified, responsible, and not acting under the direction of the surgeon in carrying out the purpose of his employment."[2] Also, "a physician who merely administers the anesthetic to a patient who is operated on by another is not liable for the negligence of the operating surgeon."[3]

Malpractice has been defined as the treatment by a physician in a manner contrary to accepted rules, and with injurious results to the patient.[4] Also malpractice signifies bad practice by individuals treating injuries to human body, either through lack of skill or neglect to apply it.[5] Therefore, the legal duty of the physician requires that the physician undertaking the care of the patient possess, and exercise, that reasonable and ordinary degree of learning, skill, and care commonly possessed and exercised by reputable physicians practicing in the same locality, or in similar localities, in the care of similar cases.[1,6] The law requires that each person act with due care toward his fellows. Failure to act so constitutes negligence, since negligence is defined as the omission to do something which a reasonable man, guided by those ordinary considerations which ordinarily regulate human affairs, would do, or the doing of something which a reasonable or prudent man would not do.[7] A physician is not presumed to be engaged for extraordinary skill or for extraordinary diligence of care, nor is the result of his treatment determinative of performance of the physician's obligation, because a doctor is not chargeable with negligence just because the result is not what is desired.[8] At the present time the physician is held not to be an insurer or guarantor of the results of his treatment, unless he specifically contracted to effect a certain result. A good result is not impliedly guaranteed.[9] However, a greater degree of skill is required by the law of the medical practitioner who specializes in any branch of his profession than is required of the physician who engages in general practice,[10] because the specialist must exercise the degree of skill which is ordinarily exercised by specialists in the same field of practice in the same or similar localities.

Consent for any operation or treatment is essential, and failure to obtain this constitutes trespass or technical assault. Any operation performed on an adult of sound mind without the adults' consent, or over his protest, constitutes actionable "assault and battery."[11] Verbal consent is considered adequate by law, but since proof of verbal consent is very difficult and sometimes impossible, it is recommended that written consent be obtained from the patient (adult) of sound mind or of the responsible person in the case of a minor or an adult of unsound mind.

The principle of "res ipsa loquitor" is a doctrine of law which has been invoked in

*Read before the Section on Anesthesiology, Southern Medical Association, Fifty-Second Annual Meeting, New Orleans, La., November 3-6, 1958.

some cases, although it was formerly not applied in malpractice cases. This is a doctrine of the general law of negligence since it is the rebuttable presumption that the defendant was negligent, which arises upon proof that instrumentality causing injury was in defendant's exclusive control and that the accident was one which ordinarily does not happen in the absence of negligence.[7] This principle relieves the patient of the necessity of proving the alleged malpractice and places on the physician the burden of making the explanations necessary to offset the implied negligence. This principle of "res ipsa loquitor" should be of special interest to anesthesiologists since this doctrine is generally applicable when the injury complained of in the malpractice case was received when the patient was unconscious.[12] A patient injured while unconscious on an operating table in a hospital could hold all, or any, of the persons who had any connection with the operation even though he could not select the particular acts by the particular person which led to his disability.[13]

All of the preceding statements have been made as referring to all physicians, and this is exactly what they do—they apply to all physicians, including anesthesiologists. It now becomes a question of what we, as anesthesiologists, can do to help protect ourselves from these nuisance, injurious, and costly suits of malpractice and trespass. The first, and most obvious, answer to this is that we must practice as reputable physicians and exercise our best judgment at all times. It would, however, be completely unrealistic to assume that any course of conduct on the part of the physician would prevent his being sued for malpractice. Good medical practice in itself is not enough; the physician must be able to defend his actions by proof of what he has done. Under present circumstances it is absolutely foolhardy for any physician to be ignorant of, or careless of malpractice prophylaxis.[14] A single careless statement even expressed as "hindsight" or "admission" of fault, might invite a claim of liability for damages where actually no liability exists because good medical practice has been followed.

The role of the anesthesiologist as a specialist today[15-17] has created problems specifically for the anesthesiologist. This has also resulted in suits against anesthesiologists which formerly might have been asserted against the operating physician. With this in mind let us list a few of the allegations set forth in the plaintiff's complaints:

1. Too much anesthetic.
2. Death from anesthetic.
3. Injury to eyes or skin.
4. Injury from mask.
5. Injury from mouth gag.
6. Injury from improper position on table.
7. Injury from struggling (Improper administration)
8. Pneumonia caused by fluid ether in lungs.
9. Anesthesia (spinal) administered without consent or against wishes.
10. Injury from spinal anesthetic.
11. Responsibility in Recovery Room.
12. Injury to teeth.
13. Fires and explosion.

This is only a partial list of allegations brought against anesthesiologists in recent years, and as time goes on the list gets longer and more varied. The problem of professional liability must be considered as an occupational hazard for every physician. Only by practicing with utmost diligence and care, observing conservative principles, and procedures which have stood the test of time, can the physician bring his untoward results and complications to their irreducible minimum.[18]

Prevention is the best, perhaps the only, defense against malpractice. The preventive measures outlined below are some of the recommendations found to be effective in the solution of the malpractice problem:

1. The physician should pay careful attention to the requirements of good medical practice.
2. The physician must know his legal duties to the patient.
3. Criticism of the work of other physicians must be avoided.
4. Good medical records should be kept. This means good anesthesia records also.
5. The physician should avoid promising the patient too much or of guaranteeing results.
6. The physician should always secure written consent for operation and anesthesia.
7. The physician should keep inviolate all confidential communications.
8. The physician should frequently check the condition of his equipment and make use of every available safety installation.
9. Upon being advised of even the possibility of a suit, the physician should notify his insurance carrier or consult with his attorney.
10. The physician should have sufficient and

proper medical malpractice insurance coverage to prevent financial ruin if professional liability charges are brought against him.

11. Consultation by the anesthesiologist with the patient regarding the anesthetic prior to premedication and surgery will help to avoid misunderstandings regarding the anesthetic given.

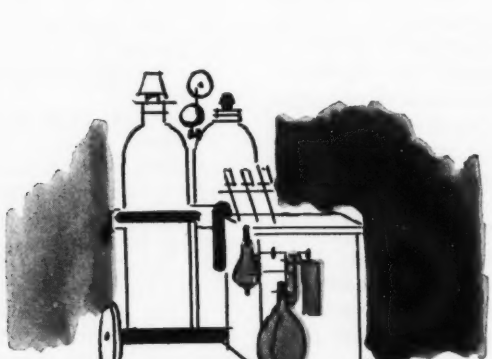
As stated above these are some of the recommendations which have been found effective in the solution of malpractice problems. The list is not all inclusive, and cannot be made so, but these recommendations apply to all physicians, and not only to anesthesiologists.

In *conclusion,* an additional thought should be injected into this discussion. It has been suggested that malpractice cases be taken away from the courts and placed in the hands of a commission similar to the commission which handles workmen's compensation. This statement was made by Howard Hassard, counsel for the California Medical Association: "There are many people, including a number of lawyers, who believe that in the course of time society must take care of disabling (medical) injuries on the same basis (that now applied to) industrial injuries—that is, the workmen's compensation system." Plaintiff's Attorney Lewis Lercara added: "I think that ultimately—it may be twenty years from now—we'll have some sort of system whereby people who are injured are going to be paid, (without) counting the fault one way or another. From the social standpoint, I think that probably it's very desirable." The consensus of several medicolegal experts is that such a plan might end the current trend of high malpractice judgments. It might also help remove the stigma now attached to a doctor whose patient is injured.[19]

Finally, I would like to point out that the discussion of medicolegal problems cannot be limited to anesthesiologists. The same legal principles and doctrines apply to all physicians. These principles in general have been presented with some special references to anesthesia.

References

1. Reagan, Louis J.: Doctor and Patient and the Law. 3rd Ed., 1956.
2. Wiley v. Wharton (Ohio)—41 N.E. (2nd) 255.
3. Nelson v. Sandell (Iowa)—209 N.W.—440. Robinson v. Crotwell (Ala.)—57 So. 23.
4. Napier v. Greenzwieg, 356 Fed. 196.
5. Isenstein v. Malcomson, 243 N. Y. S. 52.
6. Forthofer v. Arnold (Ohio)—21 N.E. (2nd) 869.
7. Black's Law Dictionary—3rd Ed.
8. Deu v. Bonney (Wash.)—231 Pac. (2nd) 637.
9. Dunn v. Beck (Mont.)—260 Pac. 1047.
10. Stern v. Lanng (La.)—31 So. 302.
11. Donald v. Swann (Ala.)—137 So. 178.
12. Pendergraft v. Royster (N. C.)—166 S.E. 285.
13. Morris, R. Crawford: "Res Ipsa Loquitor"—Liability Without Fault, J.A.M.A. 163:1055, 1957.
14. Reagan, Louis J.: A Report of the Committee on Medicolegal Problems, American Medical Association, 1951.
15. Hayt, E., Hayt, L. R., and Groeschel, A. H.: Law of Hospital, Physician, and Patient, 2nd Ed., 1952.
16. Tovell, R. M., and Steven, R. J. M.: Anesthesiologist in the Role of Anesthesia of Today, J.A.M.A. 141:8, 1949.
17. Spain v. Burch—154 S.W. 172.
18. Sadusk, Joseph F., Jr.: Hazardous Fields of Medicine in Relation to Professional Liability, J.A.M.A. 163:953, 1957.
19. Medical Economics—Sept. 1, 1958.



Tympanoplasty Class III in Teaching Mastoidectomy Operations*

GEORGE D. LYONS, M.D.,† *New Orleans, La.*

Improvement in operative technics permits the use of tympanoplasty as a means to attain better results than in the former unmodified mastoidectomies.

Introduction

FOLLOWING WORLD WAR II, German Otologists Wullstein[1] and Zollner[2] began reconstructive surgery of the middle ear and tympanic membrane. This was both for the diseased ear as well as for the traumatized ear from bomb-blast. This work was not new, however, for the first myringoplasty was reported by Berthold,[3] in 1878. The first tympanoplasty *per se* was performed in 1892, consisting of myringostapedopexies and myringoincudopexies. The success of these procedures was questionable. With the introduction of stapes mobilization, the project was abandoned until 8 years ago, when it was again resumed.

The primary goals of tympanoplasty are to eliminate middle ear disease and to salvage or improve hearing. This is attained by obtaining sound pressure transformation to the oval window and sound protection to the round window. Pressure transformation is normally accomplished by the area ratio of the tympanic membrane to the footplate of the stapes which is normally a 1:17 ratio. The other means is by the lever action of the ossicular chain which is a 1:1.3 ratio. Together these account for 25 to 30 decibel hearing loss if they are inactive. The sound protection to the round window accounts for plus or minus 30 decibel hearing loss if this function is lost.

The patient to be a candidate for tympanoplasty must be evaluated completely. He must have at least the following:

1. Pure tone audiogram.
2. A second pure tone audiogram with a patch over the perforation with a cotton pledget or paper.
3. Cochlear function must be adequate.
4. Acoustic probe test if available.
5. Eustachian tube must be patent.
6. Complete microscopic examination of the middle ear and removal of all diseased bones, cells, ossicles and mucosa. The idea is to accomplish tubal ventilation of the middle ear, sound protection to the round window and improved sound pressure transformation to the oval window.

The only contraindications to tympanoplasties are active intracranial disease or cochlear dysfunction.

There are five types of tympanoplasties. These are the following:

1. The simplest type is the myringoplasty in which there is an intact ossicular chain, a central type perforation, patent Eustachian tube and a mobile stapes. In this the pressure transformation to the oval window and sound protection to the round window is obtained.

2. This is the same as in (1) except that there is a defect in the ossicular chain, but there is a functioning incus and stapes and intact epitympanum. Again pressure transformation to the oval window and sound protection to the round window is obtained.

3. This is the most common of all the types; there is a narrowed middle ear, loss of epitympanum, and usually there is a cholesteatoma or active disease of the mastoid cells. The object here is to create a columellar or stapediopexy, and again obtain pressure transformation to the oval window and sound protection to the round window. In this case there is a loss of the lever action or the mechanical advantage of the ossicular chain which has 1:1.3 as previously described, and therefore a 20-30 decibel loss.

4. In Type 4 tympanoplasty there is no obvious ossicle chain—only a movable footplate of the stapes and this is allowed to be exposed to sound. No graft is placed against it. The middle ear consists primarily of the tubal area, the hypotympanum, and the round window area. In this type one obtains sound protection to the round window but no pressure transformation to the oval window.

5. This type is similar to Class 4, except the foot-

*Read before the Section on Ophthalmology and Otolaryngology, Southern Medical Association, Fifty-Second Annual Meeting, New Orleans, La., November 3-6, 1958.

†From the Department of Otorhinolaryngology, Louisiana State University Medical Center, New Orleans, La.

plate is not movable and a graft is placed over the footplate as the first procedure. Approximately 5 weeks after the primary operation the patient is again brought to surgery and the previous graft is elevated and a fenestration operation is performed.

Review of Cases

In this presentation 15 cases will be reviewed in which tympanoplasty Class III were performed. These patients were candidates for mastoidectomy. The diagnosis was made from x-ray studies of the mastoid, the presence of cholesteatomatous type material in the middle ear, destruction of the external ear canal, marginal or attic perforations, destruction of the ossicular chain and long histories of chronic draining ears which failed to respond to medical therapy. They qualified for tympanoplasty III in that they had evidence of cholesteatoma or marked destruction of the middle ear, but with patency of the Eustachian tube and cochlear function.

The technic used in these cases was the following:

Routine endaural incisions after Lempert[4] or House[5] were used. Mastoid cavities were completely exenerated by means of the external or transtympanic mastoid approaches. The middle ear was completely cleaned of diseased ossicular remnants and cholesteatoma. Typmpanic membrane remnants were preserved when possible. The stapes was preserved and mobilization ascertained. All of this was done with the aid of the Zeiss microscope. A thin full thickness postauricular skin graft was taken, and small squares of Gelfoam soaked in penicillin were packed in the hypotympanic area about the round window and extending to the tubal area. The graft was then applied over the anterior, inferior and superior canal wall, allowing this to fall over the promontory in contact with the capitulum of the stapes, over the facial ridge and into the mastoid cavity. In three of the four cases a polyethylene tube No. 18 was inserted into the orifice of the Eustachian tube and allowed to come out through the nose. The graft was maintained in position by small cotton pledgets. A mastoid silk sleeve was applied over these cotton pledgets and synthetic sponges inserted within this sleeve. The incision was closed and a mastoid dressing was applied.

Endotracheal anesthesia of sodium thiopentothal and nitrous oxide was used for the entire procedure.

Table 1 reviews 15 cases in which this procedure was performed.

TABLE 1

CASE REPORTS

Case	*Procedure*	*Postoperative Dry Ear*	*Hearing Tone Average* Preoperative*	*Postoperative*	*Complications*
I	Tympanoplasty Class III	Dry	35dB	30dB	None
II	Tympanoplasty with polyethylene catheter	Dry	40dB	30dB	None
III	Revision old modified radical converted to Tympanoplasty III	Wet	50dB	70dB	Vertigo 2 mos. postoperative; sloughed graft
IV	Tympanoplasty III	Wet	50dB	50dB	Sloughed graft
V	(1) Revision simple mastoidectomy (2) Decompression and neurolysis facial nerve (3) Tympanoplasty Class III	Dry	60dB	35dB	Complete facial palsy after surgery for 5 mos.; now has returned to function better than preoperatively
VI	(1) Incision and drainage subdural abscess (2) Facial nerve decompression (3) 2nd stage Tympanoplasty III	Dry	50dB	35dB	12 days between the two operations; facial nerve has returned to complete function
VII	Tympanoplasty III	Wet	35dB	35dB	Sloughed graft
VIII	Tympanoplasty with polyethylene catheter	Dry	40dB	25dB	None
IX	Tympanoplasty III	Wet	40dB	40dB	Sloughed graft and dehiscence of postauricular wound
X	Revision simple mastoidectomy to Tympanoplasty III with polyethylene	Dry	35dB	25dB	Small tubal perforation in graft
XI	Tympanoplasty III	Dry	50dB	25dB	None
XII	Tympanoplasty III	Dry after one month	35dB	30dB	Healing slow, required intensive treatment to preserve graft
XIII	Tympanoplasty III	Dry	45dB	25dB	None
XIV	Tympanoplasty III	Dry after 6 wks.	40dB	35dB	Dehiscence of, postauricular wound and partial slough
XV	Tympanoplasty III	Dry	40dB	30dB	None

*dB = decibels

The analysis of the 15 cases reveals the following:

Eleven have primary disease qualifying for tympanoplasty III. Three cases were revisions of previous mastoid operations, one from a modified radical mastoidectomy and two of simple mastoidectomies, one being a facial nerve decompression and neurolysis. Another patient had an incision and drainage of a subdural abscess, and in addition a facial nerve decompression and a second stage tympanoplasty Class III.

It will be noted that 10 patients have had good results and at present have dry ears and improved hearing. Of these 10, three have complications, ranging from recurrent bouts of otitis media responding to medical therapy, to a small tubal perforation of the graft. Dehiscence of the postauricular wound occurred in 3 cases. In 5 cases the operation was not successful in this series, and one was made worse. In the successful cases the postoperative level of hearing has ranged from 5 to 25 decibel improvement of pure tone average in the speech frequencies. The last operation was performed about 7 months ago, the first approximately 12 months ago.

Preoperative cultures were made, material from the draining ear, sensitivity tests were done and proper systemic antibiotics used prior to and following the surgical procedure. The packs were removed approximately one week after operation, the ears cleaned, and the patients were instructed not to blow their nose or sneeze with their mouth closed. They were hospitalized during this time. On the tenth postoperative day, after adequate inspection, the revised middle ear was lightly inflated by means of the Eustachian tube catheter. In the cases in which the polyethylene tubes were inserted within the Eustachian tube, the tubes were aspirated and the new tympanic membrane was inflated. All patients were followed at weekly intervals at which time the Eustachian tube was inflated. Approximately 6 weeks after the procedure, audiograms were performed.

Comment

Tympanoplasty was introduced to our resident service at Charity Hospital following the acquisition of a Zeiss operating otoscope. Prior to this time we were limited to the use of procedures of the modified radical and the radical mastoidectomy. With these new procedures, and more specifically with the additional magnification, we are now able to better exenerate disease, do a more thorough mastoidectomy, and with a higher incidence of dry ears. We may be considered more radical in our approach to this problem than many of the investigators writing today. However, because of the type of our clientele and limitations in follow-up, we feel it is safer to be radical and prevent further complications. Mastoidectomy, as such, should not be taught as the procedure of choice for disease of this middle ear, but should be reserved for those cases which do not qualify for any type of reconstructive middle ear work. Tympanoplasty should be taught and incorporated at the very beginning of residency training in conjunction with the allied specialty of audiology, and care of simple otitis media. The newer concepts of the physiology of the middle ear should also be instituted on the earliest possible level of teaching.

Summary

Tympanoplasty has been reviewed from its developmental aspects, goals, types, accomplishments, and evaluation of patients. A review of 15 cases of tympanoplasty Class III with their qualifications, technic, and follow-up study of complications have been presented. It has also been brought to the mind of the reader that tympanoplasty should be taught in the earlier levels of teaching, and that our previous destructive procedures of the middle ear must be reserved only for those cases in which no other procedure can be used.

References

1. Wullstein, H.: Theory and Practice of Tympanoplasty, Laryngoscope 66:1076, 1955.
2. Zollner, Fritz: The Principles of Plastic Surgery of the Sound Conducting Apparatus, Laryng. & Otol. 69:637, 1955.
3. Berthold, E.: (a) Ueber Myringoplastic, Wien med. Bl. 1:627, 1878; (b) Ueber Myringoplastic Med. Chi., Wien XIV, 195, 1879.
4. Lempert, J. Julius: Endaural Subcortical Mastoidotympanectomy for Cure of Chr. Persistent Suppurative Otitis Media, Arch. Otolaryng. 49:20, 1949.
5. House, Howard P.: Surgery of the Chronically Draining Ear, Arch. Otolaryng. 49:135, 1949; Surgical Repair of Perforated Ear, Ann. Otol. Rhin. & Laryng. 62:1072, 1953.

Four Years Experience with a Cobalt Unit*

PATRICK CAVANAUGH, M.D.,† *Louisville, Ky.*

Teletherapy with radioactive cobalt is being used more commonly. The author discusses several aspects of this type of irradiation.

SOMEONE HAS SAID that every major therapeutic idea passes through three phases; an initial period of enthusiastic and wide application, an interval of disenchantment, and finally into a phase of reasonable use. What was true for sulfonamides was also true for x-ray therapy itself. The tendency toward such a pattern has become evident in reviewing four years experience with a cobalt-60 unit in Louisville General Hospital. It is hoped that a resumé of our experience might be of some value to the many radiologists who will in the near future be using Co^{60} for the first time. Teletherapy is now passing from the stage of pilot operation in university centers and cancer hospitals to a phase of much wider use in general medical and surgical hospitals and even private offices. It is expected that more than 150 units will be installed this year, and that the supply of high specific activity cobalt will be in excess of the actual need from now on.[1]

While it is not possible at this time to present the results of cobalt therapy in terms of 5 year cures, we may draw some reasonably valid conclusions from our experience thus far regarding selection of patients, changing concepts of dosage, and the clinical usefulness of commercially available equipment. Furthermore, we have had an opportunity to re-evaluate the purely theoretical advantages and disadvantages of cobalt therapy postulated by Brucer and others in the early 1950's. It is now possible to say whether some of these appear to be clinically significant or not.

Selection of Patients

In retrospect it appears that we began using cobalt with two aims in mind: (1) to improve the treatment of lesions for which radiation was traditionally indicated, and (2) to increase the range of indications for radiotherapy. That there was predominant emphasis on the latter possibility was evident from our first 100 patients, 91 of whom were candidates for palliative therapy only, or in many instances for no radiation therapy. Post-irradiation recurrences formed a large group; gastrointestinal lesions, advanced ovarian tumors, traditionally resistant tumors of the central nervous system, and a number of deplorably advanced oropharyngeal lesions typified the group. It is interesting that significant survival or palliation was seen only in those patients who could be expected to benefit from conventional radiotherapy. Admittedly, none of the features of cobalt-60, such as increased depth dose, skin-sparing, or low integral dose could be expected to alter the basic facts of radiobiology that were described 30 or more years ago. A significant factor in the referral of poor material was the publicity attending installation of the unit. Many of our most advanced cases were patients who had read about the cobalt machine in the newspaper. A typical argument of the physician referring a poor case was the statement: "It may not help but what have we got to lose?" The answer soon became evident that where nothing is gained we may possibly have lost a great deal by consistently associating our potentially best form of treatment with the most hopeless cases. Over a period of time the predominant interest shifted toward improved treatment of lesions for which radiotherapy was already the treatment of choice. Although it is not possible to speak of the value of Co^{60} in terms of 5 year results, it is a fairly safe prediction that when the 5 year results are published they will not be dramatically

*Read before the Section on Radiology, Southern Medical Association, Fifty-Second Annual Meeting, New Orleans, La., November 3-6, 1958.

†From the Department of Radiology, University of Louisville School of Medicine, Louisville, Ky.

improved. We can definitely state that the morbidity and sequellae of cobalt irradiation can be dramatically less than with conventional therapy. This may have an indirect effect on the 5 year cure rate by encouraging more patients to be treated by radiation where it is indicated. The fixed idea that radiation is associated with skin burns and nausea so common to the majority of patients and a surprising number of referring physicians is now much less of a problem. Without a doubt surgeons are now referring better material than when conventional therapy was available. They have found, for instance, that it is possible to operate in a rather heavily irradiated area without the fear of skin breakdown, thus opening to reconsideration the much discussed question of preoperative irradiation.

In general, our selection of patients for treatment with the cobalt machine remains the same as for a conventional unit. Field arrangements are of course modified, and higher dosages as well as dose rates are employed. For example, in carcinoma of the cervix the parametrial dosage we have employed equals or exceeds the limits of tolerance suggested by Garcia and others for conventional therapy.[2] So far no ill effects have been noted from higher dosages in depth, although several obese patients have developed subcutaneous reactions. As yet we have no convincing clinical demonstration of a lower *relative biological efficiency* for Co^{60} even though a factor of 0.85 to 0.90 is commonly suggested by radiobiologic studies.

Within certain limits we have been able to expand the range of indications for radiotherapy. Tumors of known radiosensitivity may be denied sufficient conventional treatment because of location. For example, recurrent lymphomas lying under skin extensively damaged by previous irradiation have been treated without complications. Retroperitoneal metastases of moderate radiosensitivity, e.g., from embryonal carcinoma, can be given much larger doses with minimal side effects.

"Inherent" vs. Observed Peculiarities of Co^{60}

The physical nature of cobalt-60 allows some speculation concerning its clinical use, but we have found that the "inherent" advantages and disadvantages are relative both to the type of equipment and to the clinical situation in which it is used.

One still hears unqualified references to Co^{60} as being equivalent to 2 Mev. x-irradiation. This is true if reference is made to the quality of the beam, but not for depth dose except under certain conditions of source strength and distance. Two extreme varieties of commercial units available provide widely different depth doses of the same quality. Units designed for use at 80 cm. s.s.d. contain sources of 2,000-3,000 curies and provide depth doses equivalent to 2 Mev. x-rays. On the other hand, small units intended for use at 20 to 30 cm. s.s.d. contain 200 to 300 curies and provide the same depth dose as a 250 kv. x-ray machine. A third type of unit employs a middle distance of from 35 to 50 cm. and is, from the standpoint of adaptability to most patients the most useful of the three. The 10 cm. percentage depth dose for a cobalt unit operating at 50 cm. is approximately 50 per cent. Increasing the s.s.d. to 80 cm. increases the depth dose to 56 per cent. The 2 Mev. Van de Graaff generator operating at 100 cm. yields a 56% depth dose.[3] The relatively small gain of these larger units is offset by an approximate doubling of unit cost.

A few qualifying remarks should be made about the "inherent" skin and bone sparing effects of Co^{60}. Although skin reactions are generally mild we have observed severe subcutaneous fibrosis in a few patients treated with high dosages. These lesions are painful and prolonged and certainly less tolerable than conventional skin reactions. On the other hand one would not necessarily expect favorable results in treating lesions which ulcerate or infiltrate the skin inasmuch as the maximum dose is at 5 mm. depth. In actual experience this type of lesion responds just as well to cobalt as to conventional x-ray therapy.

Reduced bone absorption with Co^{60} rays does not eliminate the hazard of necrosis if the treatment is complicated by infection or trauma. Furthermore, treatment of metastatic lesions in bone gives the same response as with similar doses of conventional x-ray. We now use cobalt entirely for this type of therapy, to take advantage of the skin sparing effect. A most striking example of the differences between cobalt and conventional

therapy has been noted in giving large doses of irradiation through the eye. Provided the lid is kept open during treatment the immediate reaction is mild, but permanent changes in the conjunctiva, cornea, sclera and anterior chamber are virtually undetectable. Lens opacities develop as with other forms of therapy.

Due to the limiting factor of self absorption and specific activity the cobalt source must be at least one centimeter in diameter. The projected beam is invariably surrounded by a zone of penumbra, the size of which is constant for any given combination of source size, and source—collimator-skin distance, regardless of field size. Thus the penumbral zone becomes larger, percentagewise, as the fields become smaller. For example, in the unit we have employed the penumbra is approximately 1.5 cm. in size. This would double the treated area and volume of a 4 cm. circular field. With larger fields the penumbra is relatively small, particularly in comparison to the side-scatter around a comparable beam of 250 kv. x-ray. One encounters frequent references to the "disadvantages" of penumbra.[4] We have not encountered or heard of any effects attributable specifically to penumbra and doubt if it is of clinical importance except in the smallest fields.

Inadequate Design

In even the best commercially available unit there is a gap between what it provides and what is needed in the way of a clinically useful beam. Light localizers provide the most accurate means of projecting fields but too frequently there is a discrepancy between the light field and the radiation beam. Where cones are employed, the number of field sizes and shapes is arbitrarily limited to a fraction of those required. Further means of shaping the field with auxiliary diaphragms and wedge filters are seldom provided in commercial units but must be contrived and attached by the user. It is encouraging to note that one firm is offering a compact tungsten unit provided with a variable collimator of unique design which allows for projection of a beam any irregular shape or size.

Economy of Co^{60} vs. Supervoltage X-ray

It is not necessary to recall here the obvious advantages of cobalt-60 units in terms of initial cost and housing. However, it is worthwhile noting that radiologists frequently over-estimate their requirements in terms of source strength and output. When installing our unit containing 1,000 curies we anticipated replacing the source in 5 years.[5] It now appears that we should be able to continue treating 30 to 40 patients daily and not replace the present source before 7 or 8 years. We found that we were limited not by how many patients we could treat per hour but by how many we could talk to, examine, and write prescriptions for. To us, the most meaningful description of a cobalt unit is in terms of depth dose, not output.

In 4 years the maintenance cost on our machine totaled under 15 dollars. During the same period the price of high specific activity cobalt dropped by half.

The only significant economic problem is the necessity of discarding this cobalt source when it becomes too low in activity for efficient use. The development of internationally standardized source capsules should provide a solution for this problem by enabling the partially spent source to be transferred to a smaller unit for efficient use at shorter distance.

Summary

Four years' experience with a cobalt-60 unit is reported in terms of patient selection, unexpected clinical advantages and disadvantages, shortcomings of commercial units and cost factors.

References

1. Errington, R. F.: Outline of World Requirements for Cobalt-60 Machines, Radiology 70:481, 1958.
2. Nolan, J. F.: Cobalt-60 in Carcinoma of the Cervix, Am. J. Obst. & Gynec. 72:789, 1956.
3. Tsien, T. C., and Robbins, R.: Comparison of Co^{60} with 2 Mev. Van de Graaff Machine on the Basis of Physical Measurements, Radiology 70:486, 1958.
4. Perryman, C. R.: Advantages and Disadvantages of Co^{60}, Pennsylvania M. J. 59:1236, 1956.
5. Reeves, J. D.: Supervoltage X-ray and the Cobalt Bomb, South. M. J. 51:1183, 1958.

Further Observations on the Problems of Vesicoureteral Reflux*

C. M. PASQUIER, JR., M.D., E. C. ST. MARTIN, M.D., and J. H. CAMPBELL, M.D., *Shreveport, La.*

An effort should be made to find and evaluate obstructions of the lower urinary tract and diseases of the bladder wall which may permit ureteral reflux.

OUR INTEREST in vesicoureteral reflux, particularly in children, now extends over a period of four and one-half years (March 1954 to October 1958). Apparently, this interest is shared by many, as evidenced by the frequency with which the subject has recently appeared on the programs of the various urologic meetings.

Several aspects of this intriguing but perplexing phenomenon still await an entirely satisfactory explanation. It is only through continued investigation and accumulation of experience that these questions will be answered and the ultimate significance of reflux established. The purpose of the present writing is to supplement our previous reports with additional information gained from further investigation in the hope that it will contribute somewhat to the final clarification of the subject.

Incidence

During the last four and one-half years, we have done cystograms (including a post-voiding film when the patient's cooperation could be secured) on 500 children 12 years of age or younger. Reflux was demonstrated in 69 or 13.8% of these children. It is interesting to note that the incidence is slightly higher than that reported earlier by us from a smaller series,[1] and compares closely with that recently published by Forsythe.[2] The latter observed reflux in 61 of 445 children examined by cystography, an incidence of 13.7 per cent.

In our group of cases 53 or 83% were females. Forsythe, on the other hand, found the distribution to be equal between the two sexes.

Pathogenesis of Reflux

Most of the recent writers on the subject of reflux have made reference to the important earlier experimental work of Gruber,[3,4] and of Graves and Davidoff.[5-8] These investigators demonstrated the importance of a relatively long, intact intravesical ureter in the prevention of vesicoureteral reflux. Their observations have been given added support by the more recent studies of Hutch.[9] The latter has presented forceful evidence for his theory that reflux results when changes in the bladder wall allow the intravesical segment of the ureter to assume an extravesical position (Fig. 1). This has been observed to occur in some of our own patients (Fig. 2).

Conditions Producing Reflux

According to Hutch's theory, several conditions may bring about the changes in the bladder wall which permit the intravesical

FIG. 1

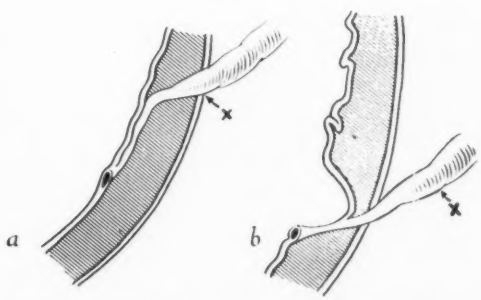
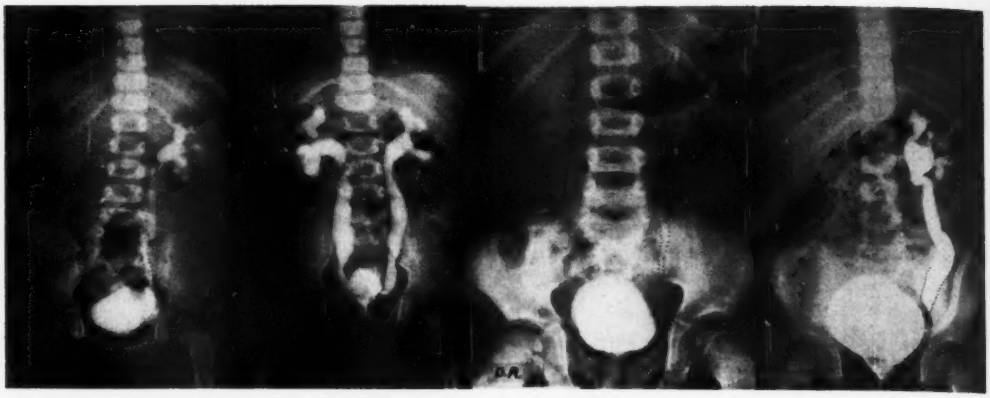


Illustration taken from Hutch's monograph "The Ureterovesical Junction," p. 60. (Courtesy of Dr. Hutch and the University of California Press.) (a) Demonstrates normal relations of the intravesical ureter. (b) The relations of the intravesical ureter after changes in the bladder wall which permit it to become extravesical.

*Read before the Section on Urology, Southern Medical Association, Fifty-Second Annual Meeting, New Orleans, La., November 3-6, 1958.

FIG. 2



Cystograms demonstrating reflux and the "notch sign" near the ureterovesical junction as described by Hutch. This is thought to be produced by "extravesicalization" of the intravesical ureter.

ureter to become extravesical and thereby result in reflux. In one category may be placed the conditions which produce a thickened, trabeculated bladder, namely, spastic neurogenic bladders and obstructions of the bladder neck or infravesical ones. In the other category may be placed conditions which produce a thin-walled, dilated bladder, such as in atonic neurogenic bladders and myogenic atonia (Fig. 3). This classification, it will be seen, includes the generally recognized causes of reflux, with the exception of infection and trauma of the intravesical ureter. Presumably, the last two conditions may lead to the development of reflux through changes in the intravesical ureter which prevent it from collapsing as the bladder fills.

In the present series, neurogenic dysfunctions (both hypertonic and atonic) of the bladder accounted for 2, or only 3% of the cases of reflux. Obstruction of the bladder neck or other infravesical obstruction was judged to be the fundamental cause in 66, or 96 per cent. While infection was present in 58 or 84% it was usually in association with obstruction of the bladder neck. Infection alone was responsible for only one or one per cent of the cases of reflux (Fig. 4).

In every instance we have been able to demonstrate an adequate cause for the reflux. Forsythe, however, reports that he was unable to find any other abnormality of the urinary tract in 30, or almost 50% of his cases. He states further that lower urinary tract obstruction is not a common cause of vesicoureteral reflux in children. This is, of course, at variance with our own experience which seems to point to obstructions of the bladder neck and other infravesical ones as the outstanding cause of reflux in children.

Admittedly, the cystoscopic diagnosis of obstruction of the bladder neck in children, particularly in girls, is difficult. However, we feel that observance of the following points in the technic of examination will facilitate the recognition of this condition.

1. Adequate distention of both the bladder and the posterior urethra with irrigating medium.

2. Use of the #24 F. McCarthy panendoscope whenever possible in females.

3. Careful search for indirect evidence of infravesical obstruction, namely, trabecula-

FIG. 3

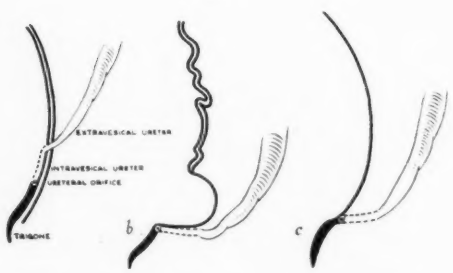
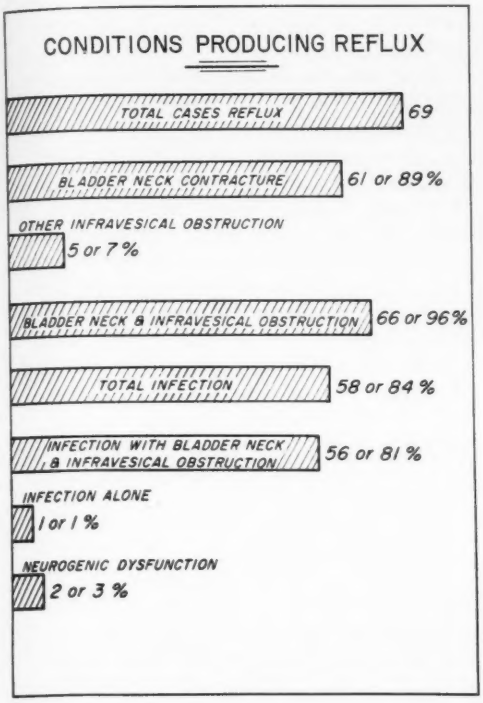


Illustration taken from Hutch's monograph "The Ureterovesical Junction," p. 164. (Courtesy of Dr. Hutch and the University of California Press.) (a) Demonstrates the normal relations of the intravesical ureter. (b) The bladder wall change that occurs in thickened, trabeculated bladders permitting the intravesical ureter to become extravesical. (c) The bladder wall change that occurs in thin-walled bladders permitting the intravesical ureter to become extravesical.

FIG. 4



tion, cellules, and diverticula. On a few occasions we have been able to observe the saccule adjacent to the intravesical ureter described by Hutch.

4. Gentle manipulation of the panendoscope at the region of the bladder neck to elicit a sensation of resistance.

5. Careful inspection of the anterior half of the bladder neck. "Anterior lip" types of obstruction have been observed in several patients.

Failure to have followed the above points, we believe probably would have resulted in overlooking a number of cases of bladder neck obstruction.

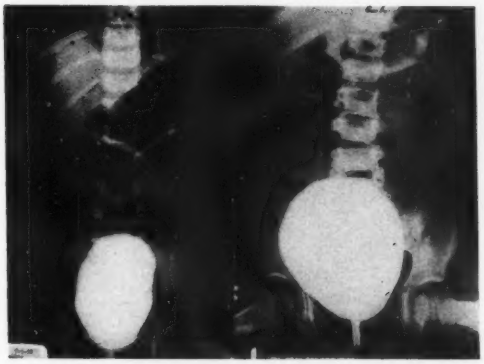
Significance of Reflux

This is probably the most controversial aspect of the entire problem. To settle this point, as to the significance of reflux, would seem to be of the utmost importance. Once this has been accomplished we will be able to view this relatively frequent phenomenon in children in its true perspective.

Initially, it was our impression that all observed reflux was significant and that, unless active measures were taken to correct it, serious damage to the upper tract would result. However, we now believe this is not universally true for two reasons: (1) The relative frequency of reflux that we and others have observed in children must have always existed. There is no reason to believe that this is a new phenomenon. Only the awareness of it is new. Certainly, if all cases of reflux proceeded relentlessly to damage of the upper tract, we would be seeing a great many more cases of such damage in adults as an end result of unrecognized reflux persisting since childhood. (2) In our own experience we have seen reflux disappear spontaneously in at least three children who had received only conservative therapy.

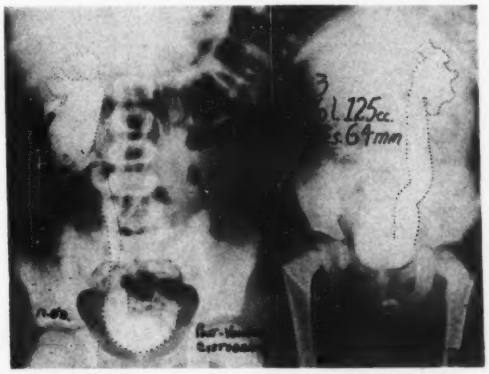
On the other hand, it is a well-established

FIG. 5



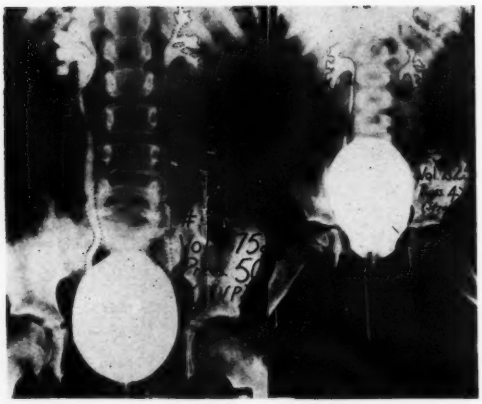
Cystograms of patients with reflux demonstrating "minimum findings."

FIG. 6



Cystograms of patients with reflux demonstrating "maximum findings."

FIG. 7



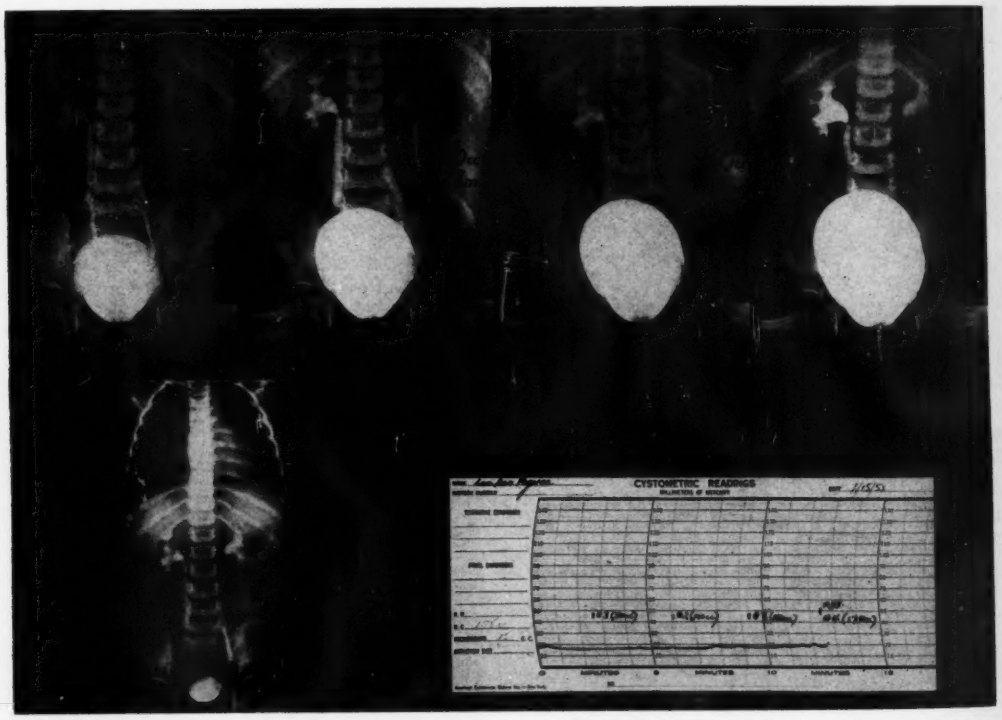
Cystograms of patients with reflux demonstrating "intermediate findings."

fact that certain cases of vesicoureteral reflux will progress to the point of severe damage to the upper urinary tract unless the process is reversed. Further, as previously reported by us,[1] reflux may persist after removal of the fundamental cause. Such cases require definitive surgical measures to correct the reflux *per se*.

How, then, can one decide at the outset, if possible, which patients can be handled expectantly and which ones demand an all out effort to abolish the reflux?

In the two extreme types of cases, that is, those with minimum and those with maximum findings, the decision regarding the reflux is not difficult to make. In the former (Fig. 5), treatment of the fundamental condition, usually either infravesical obstruction or infection or a combination of both, will usually be sufficient. The reflux here may be expected to either disappear completely or, if it persists, remain at a static level and pose no further problem. In the latter (Fig. 6), that is patients with maximum findings, it is usually quite evident that correction of the fundamental cause alone, such as obstruction of the bladder neck, will not be

FIG. 8



Combined serial cystogram and cystometrogram illustrating the early development of reflux with a small amount of fluid in the bladder and a normal intravesical pressure.

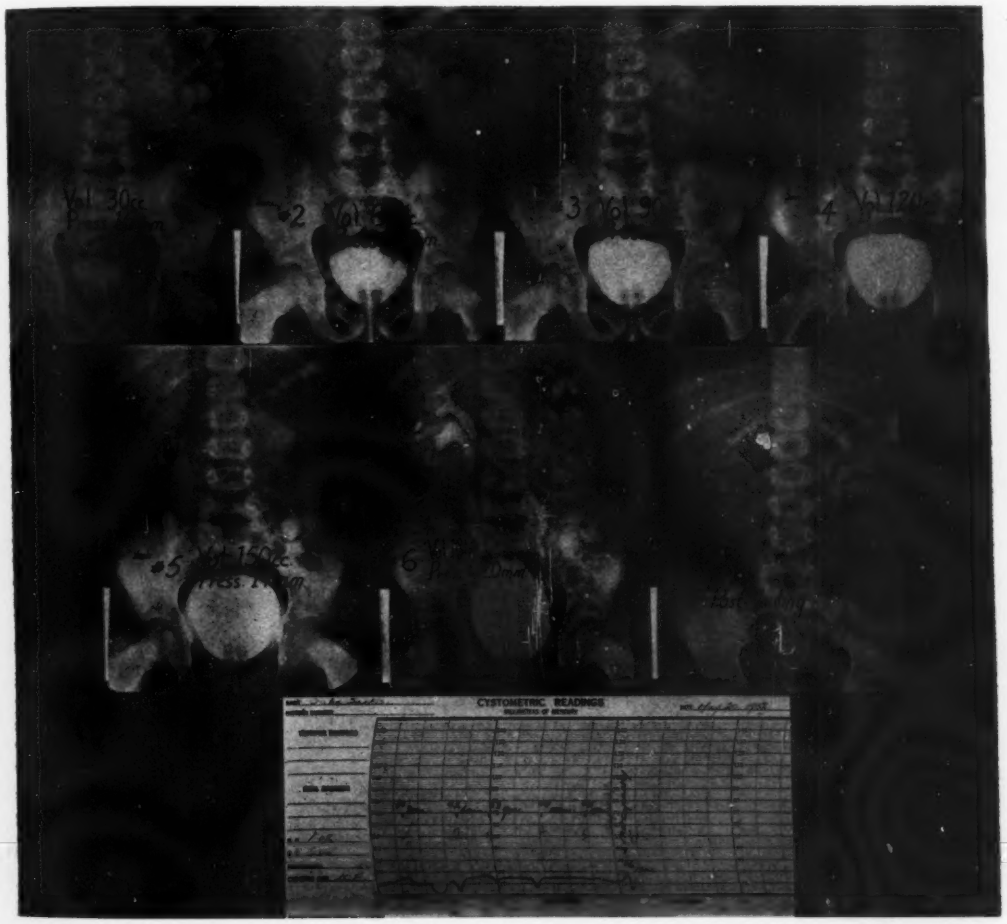
sufficient. Here one can anticipate such marked changes at the ureterovesical junction that reflux will persist unless an attempt is made to re-establish the normal anatomic and physiologic condition of the intravesical ureter.

Unfortunately, the situation is not always so clear-cut. Not infrequently one encounters patients with findings intermediate between the above described extremes (Fig. 7). It is in cases just such as these that we have our greatest difficulty in judgment. Should we simply correct the fundamental problem and observe the progress of the reflux, or should we also perform definitive surgery initially, such as the Hutch vesicoureteroplasty, to insure that reflux will not persist and be a source of further disability in the urinary tract?

It would seem that the key to the solution of this problem might be found if we had some means of determining whether or not irreversible changes in the condition of the intravesical ureter had occurred.

As previously reported, we[1] have had a limited experience with combined serial cystograms and cystometrograms. This specialized procedure was originally done on some of our patients in an attempt to learn what part, if any, variations in intravesical pressure played in the development of reflux. No consistent relationship could be estab-

FIG. 9



Combined serial cystogram and cystometrogram illustrating the late development of reflux only as the bladder capacity is approached and the intravesical pressure raised by voluntary straining.

lished. It was observed, however, that in some patients reflux developed almost immediately with small amounts of fluid in the bladder and normal pressures. Others showed no reflux until the capacity of the bladder was approached and the pressure rose either spontaneously or by voluntary straining (Figs. 8 and 9).

We have continued the use of this procedure in certain cases as we have attempted to investigate the problems of reflux further. Again, a tendency has been noted for patients to exhibit one or the other of these two patterns of behavior. The possibility came to mind that these observations might have some practical application in determining the condition of the intravesical ureter. Possibly those patients who have reflux with small volumes and low pressures are those in whom more marked changes in the intravesical ureter have occurred so that the ureterovesical valve mechanism has become totally incompetent. On the other hand, those who show reflux only as the bladder reaches capacity and the intravesical pressure is raised may represent patients in whom marked changes in the intravesical ureter and total incompetency have not yet occurred.

Experience along these lines of investigation has not been extensive enough to permit any very positive statement as to the ultimate value of combined serial cystograms and cystometrograms in determining the condition of the intravesical ureter. However, it is planned to continue these studies in the hope that they may make some contribution to the solution of this aspect of the reflux problem.

It would seem also that if irreversible changes in the intravesical ureter have occurred, one might expect this to be reflected in the appearance of the upper urinary tract on pyelography. Hutch has demonstrated that an intravesical ureter which has become extravesical ultimately develops into a secondary obstructive factor with resulting progressive dilatation of the urinary tract above (Fig. 10).

A review of our own cases has shown a high incidence of changes in the upper tract in the initial pyelograms of the patients in whom reflux persisted after treatment of the condition judged to be the fundamental cause of the reflux. On the other hand, in the group of patients whose reflux disappeared after treatment of the basic disease there were very few with pyelograms showing changes in the upper tract.

Thus, from our own observations, it would appear that changes in the upper tract shown on pyelography are the best indication that irreversible changes in the intravesical ureter may have occurred and that consequently reflux is apt to persist even though the fundamental cause is removed. At the present time, this is the criterion we are using to select the patients who should have vesicoureteroplasty to correct reflux at the outset, in addition to treatment of the condition judged to be the fundamental cause of the reflux.

The following illustrative case is briefly reported.

J. M., a 9 year old white girl, was referred for urologic investigation because of enuresis. She was found to have a contracture of the bladder neck and bilateral vesicoureteral reflux. A combined serial cystogram and cystometrogram was performed (Fig. 11). The findings were those previously referred to as being "intermediate" in degree. Reflux developed earlier on the right side and appeared to be more marked than that on the left. Excretory urograms demonstrated some dilatation of the upper tract on

FIG. 10

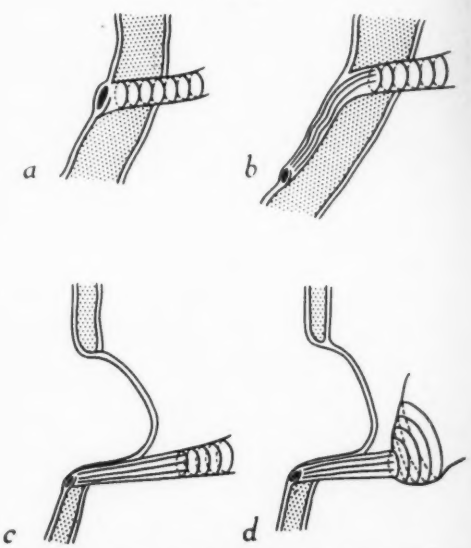
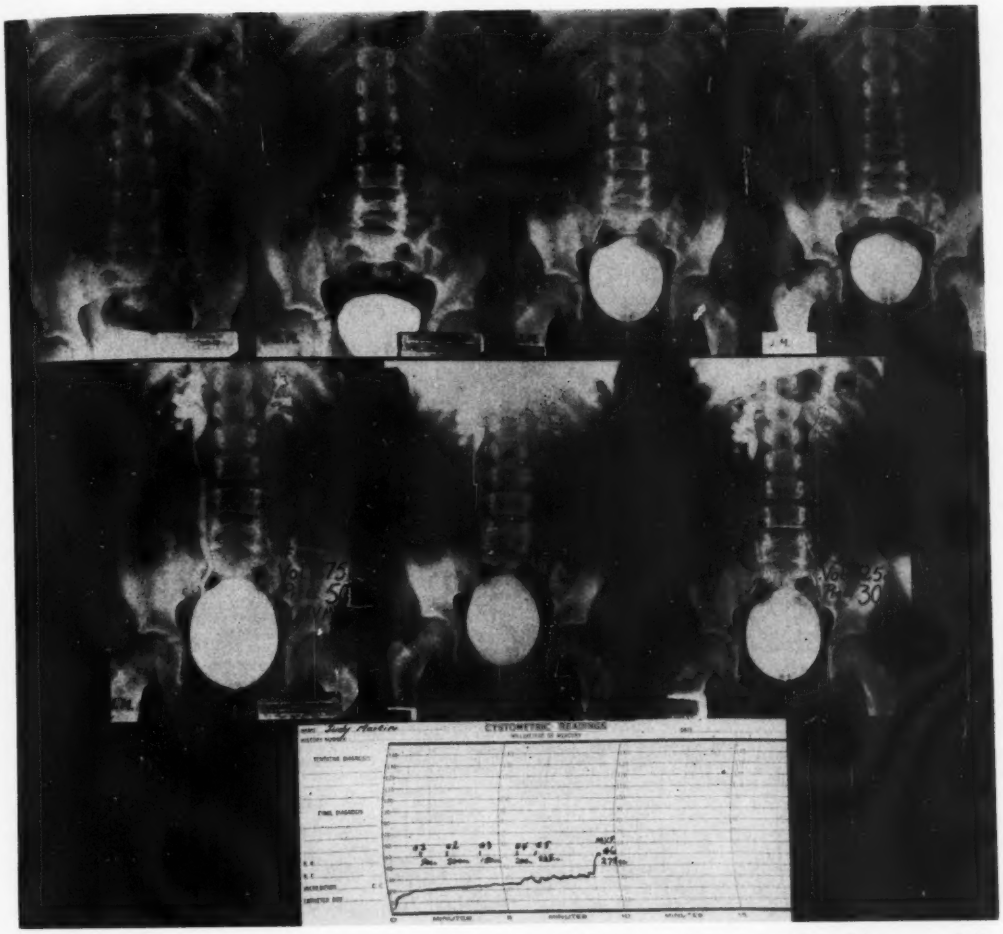


Illustration taken from Hutch's monograph "The Ureterovesical Junction," p. 67. (Courtesy of Dr. Hutch and the University of California Press.) This demonstrates the manner in which an intravesical ureter that has become extravesical develops into a secondary obstructive factor resulting in progressive upper urinary tract dilatation.

FIG. 11



Combined serial cystogram and cystometrogram. Note that reflux has developed earlier on the right and is more marked than on the left. These findings are in the category previously referred to as being "intermediate" in degree.

the right side (Fig. 12, A). A Bonin Modification of the Bradford-Young bladder neck resection was done along with a Hutch vesicoureteroplasty on the right. A postoperative cystogram reveals complete absence of reflux on the right and persistence of minimal reflux on the left side (Fig. 12, B).

Surgical Correction of Reflux

When it becomes necessary to attempt correction of the reflux *per se,* we have had good results with the Hutch method of vesicoureteroplasty. We have had no experience with the procedure more recently described by Politano.[10] However, it appears that it adheres to the same principles as the Hutch procedure and should prove to be equally successful.

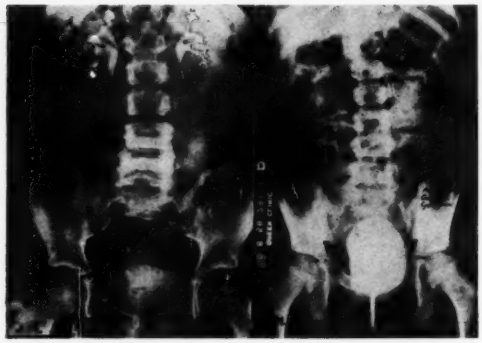
To date, we have adequate follow-up studies on 11 children in whom the Hutch operation has been performed. The procedure has successfully corrected the reflux in 10, or 91 per cent.

Summary and Conclusions

In our experience with vesicoureteral reflux in children during the past four and one-half years a frequent association between obstruction of the bladder neck and this condition has been observed.

Hutch has proposed an explanation for the reflux accompanying such obstruction based on alterations in the bladder wall which per-

FIG. 12



A B

(A) Execretory urogram (same patient as in figure 11) demonstrating dilatation of the upper urinary tract on the right side. (B) Postoperative cystogram following a Bonin Modification of the Bradford-Young bladder neck resection combined with a Hutch vesicoureteroplasty on the right side. Note that the reflux on the right side has been abolished. Minimal reflux persists on the left side.

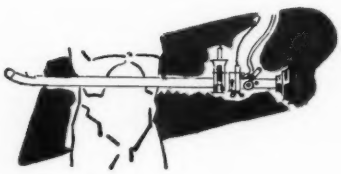
mit the intravesical ureter to become extravesical. These changes have been demonstrated in some of our patients.

All cases of reflux are significant in that they point to a more fundamental causative condition which should be searched for and treated. This having been accomplished, the associated reflux may follow any one of three courses. It may disappear completely; it may persist and be of no further consequence to the patient; or it may continue and result in progressive upper urinary tract damage. The critical factor determining which course the reflux will take appears to be whether or not irreversible changes at the ureterovesical junction have occurred.

Our present experience seems to indicate that one may predict fairly accurately the future behavior of reflux from the appearance of the initial pyelograms. If the latter show changes in the upper tract, it is very likely that irreversible changes in the intravesical ureter have occurred and that reflux will persist and be a source of further disability. Such patients will require reconstructive surgery on the ureterovesical junction to abolish the reflux. This can be accomplished quite satisfactorily by the Hutch method of vesicoureteroplasty.

References

1. Pasquier, C. M., Jr., St. Martin, E. C., and Campbell, J. H.: The Problem of Vesicoureteral Reflux in Children, J. Urol. 79:41, 1958.
2. Forsythe, W. I., and Whalen, R. F.: The Occurrence and Significance of Vesico-ureteral Reflux in Children, Brit. J. Urol. 30:189, 1958.
3. Gruber, C. M.: I. A Comparative Study of the Intravesical Ureters (Uretero-vesical valves) in Man and in Experimental Animals, J. Urol. 21:567, 1929.
4. Gruber, C. M.: III. The Function of the Ureterovesical Valve and the Experimental Production of Hydroureters Without Obstruction, J. Urol. 23:161, 1930.
5. Graves, R. C., and Davidoff, L. M.: Studies on the Ureter and Bladder with Especial Reference to Regurgitation of the Vesical Contents, J. Urol. 10:185, 1923.
6. Graves, R. C., and Davidoff, L. M.: II. Studies on the Ureter and Bladder with Especial Reference to Regurgitation of the Vesical Contents, J. Urol. 12:92, 1924.
7. Graves, R. C., and Davidoff, L. M.: III. Studies on the Bladder and Ureters with Especial Reference to Regurtitation of the Vesical Contents, J. Urol. 14:1, 1925.
8. Graves, R. C., and Davidoff, L. M.: IV. Studies on the Ureter and Bladder with Especial Reference to Regurgitation of the Vesical Contents, J. Urol. 18:321, 1927.
9. Hutch, John A.: The Ureterovesical Junction. Berkeley and Los Angeles, University of California Press, 1958.
10. Politano, Victor A., and Leadbetter, Wyland F.: An Operative Technique for the Correction of Vesicoureteral Reflux, J. Urol. 79:932, 1958.



CASE REPORT

Bronchopulmonary Moniliasis Complicated by Peritonitis: Evaluation of Treatment of Acute Bronchopulmonary Moniliasis

LAWRENCE MARYANOV, M.D.,† *Cambridge, Md.*

MONILIASIS is an acute or subacute infection of the skin or mucous membranes, by a yeast-like fungus, which may be localized to the skin, nails, mouth, vagina, bronchi or lungs. Occasionally, by invading the blood stream it localizes on the endocardium or meninges.

The monilia are inhabitants of plant life. To human tissues they are so feebly pathogenic that they are incapable of producing disease unless the tissues are devitalized by chronic disease or local trauma.

Etiology. The infection is caused chiefly by *Candida albicans,* but other species of *Candida* may sometimes be responsible. The occurrence of moniliasis is universal, and actual epidemics have occurred.

Clinical manifestations. Symptoms of moniliasis vary according to the site of infection. Oral infections take the form of thrush and show the typical creamy white patches. Intertrigo may occur in the axillas, inframammary areas, umbilicus, gluteal folds or groin. Perianal moniliasis produces pruritus ani of the white macerative type. Severe generalized cutaneous moniliasis may have the appearance of eczematoid lesions. Mycotic vulvovaginitis is relatively common and is characterized by discharge, inflammation of the vaginal wall, and white scattered confluent patches resembling thrush on the labia, vagina, and cervix.

Bronchopulmonary moniliasis in the usually mild form produces malaise, cough, mucoid sputum, and slight rise of temperature. Severe infection may cause physical signs of a confluent or lobar pneumonia. Fatal cases of septicemia, endocarditis and meningitis due to *Candida albicans* have been reported. There is nothing distinctive about the radiographic or physical findings. The diagnosis can be made only by the examination of smears and cultures of sputum.

Diagnosis. The organism may be present as a saprophyte or as a secondary invader in other diseases. Diagnosis of primary moniliasis is made by identifying *Candida albicans* in material from the lesions, by the characteristic clinical manifestations, response to treatment, and the exclusion of other underlying diseases as a cause.

Prognosis and treatment. Lesions generally respond readily to treatment, but recurrence is frequent, especially in individuals who have become hypersensitive to the organism. Severe pulmonary infections may cause death.[1]

The use of antibiotics directly stimulates the growth of fungi, normally present in small numbers in the nasopharynx and gastrointestinal tract.[2]

A small number of cases of generalized fatal moniliasis have been recorded in which the possible etiologic role of prolonged antibiotic therapy has been stressed. The existence of a large quantity of potentially pathogenic organisms in a severely ill person predisposes to infections. Fungi which ordinarily have a low degree of virulence may find conditions favorable for invasion when the host's defense is depressed by such factors as serious disease, malnutrition, surgical trauma or old age.[3] Antibiotic therapy has made it increasingly rare for patients with fatal disease to die of a

†From the Department of Medicine, Cambridge-Maryland Hospital, Cambridge, Md.

terminal bacterial infection.[4]

Monilia infections have been treated with brilliant green aerosol and with nystatin (Mycosatin) with fair results.[5]

Case Report

P. R., a white laborer, aged 28, was admitted to the Cambridge-Maryland Hospital, Cambridge, Maryland, on Sept. 20, 1958. He complained of a sudden onset of headaches, generalized abdominal pain associated with nausea and vomiting of 3 days duration. There also were "chills and fever."

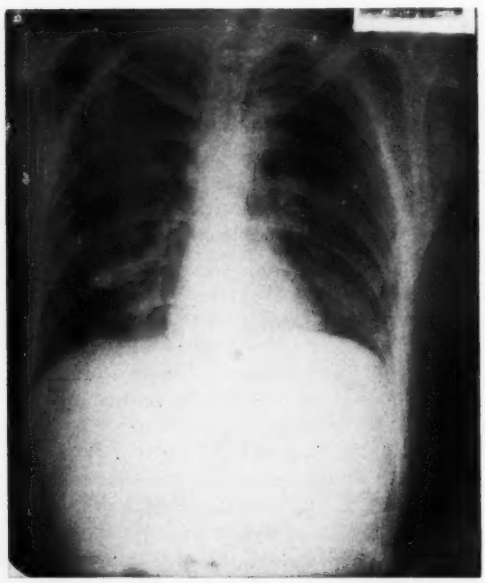
Physical examination revealed an acutely ill and very apprehensive male. The abdomen was rigid with tenderness over both upper quadrants, but more marked on the left. Temperature was 104° F., WBC 14,450, HCT. 48%; the urine was negative.

The *admitting diagnosis* was gastroenteritis.

He was placed on a liquid diet, given chlorpromazine 25 mg. q.i.d., penicillin and streptomycin, combined b.i.d., and Tr. belladonna getts. 8, every 4 hrs. During the next 2 days, the patient improved even though his abdomen was still tender upon palpation. The temperature dropped to 100° F.

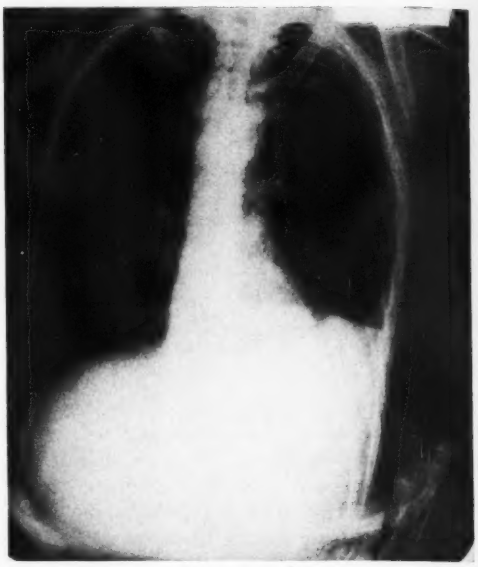
On the 3rd hospital day he began to complain of pain in his chest. Physical examination of the chest was negative. X-ray film of the chest indicated innumerable small well-defined areas of increased density, studded throughout both lungs. There was also noted an area of increased density, approximately 3 cm. in diameter in the right middle lobe, middle lung field (Fig. 1). Agglutination tests were negative. On

FIG. 1



(September 27, 1958)

FIG. 2



(October 23, 1958)

Sept. 24, 4 days after admission, the patient became confused. His temperature rose to 104° F. Free fluid was noted in both flanks. He began to vomit, and it was thought the patient had a partial paralytic ileus. Toxic psychosis developed with delirium tremens. He had auditory and visual hallucinations, and his condition was considered critical. Cheyne-Stokes respirations began and the patient was placed in an oxygen tent. Fluid was obtained by abdominal paracentesis, and *Candida albicans* was isolated from the culture. Sputum was unobtainable due to the patient's confused state. Antibiotic sensitivity tests indicated that the organisms cultured, were sensitive to sodium novobiocin (Cathomycin), nitrofurantoin (Furadantin) and Kantrex.

Because of the critical state and toxicity of the patient, he was given 80 units of ACTH daily, 50 mg. cortisone every 6 hrs.; Kantrex 0.5 Gm. q.i.d. I.M., and 180 mg. of nitrofurantoin I.V. in 1,000 cc. 10% glucose saline solution b.i.d. This treatment was based on the hypothesis that corticoids in some way exert a nonspecific antitoxic effect, protecting the cells of the host against a variety of bacteria and toxins. Within 24 hours dramatic improvement was noted.[6] The patient become alert, wished something to eat, and his temperature dropped to below 100° F.

Sputum examination showed the presence of *Candida albicans.*

Furadantin and Kantrex were continued for 2 weeks and then gradually discontinued. The steroids were discontinued after 5 days. X-ray examination of the chest on the 18th hospital day was negative (Fig. 2).

The patient began to convalesce and after 49 days was discharged from the hospital as improved.

Follow-up for the next 2 months has indicated no recurrence of symptoms. He is not taking any medication, although sputum examinations still indicate the presence of *Candida albicans*.

Summary

Bronchopulmonary moniliasis has been reported in the literature, although there have been no reports of bronchopulmonary moniliasis complicated by peritonitis due to the monilia infection.

Kantrex and Furadantin apparently were very effective in the treatment of this case of bronchopulmonary moniliasis complicated by peritonitis.

References

1. Woods, W. W., Manning, I. H., and Patterson, C. N.: Monilial Infections Complicating Therapeutic Use of Antibiotics, J.A.M.A. 145:207, 1951.
2. Seligmann, E.: Virulence-Enhancing Activities of Aureomycin on Candida Albicans, Proc. Soc. Exper. Biol. & Med. 79:481, 1952.
3. Kligman, A. M.: Are Fungus Infections Increasing as Result of Antibiotic Therapy, J.A.M.A. 149:979, 1952.
4. Brown, C., Jr., Propp, S., Guest, C. M., Beebe, R. T., and Early, L.: Fatal Fungus Infections Complicating Antibiotic Therapy, J.A.M.A. 152:206, 1953.
5. Smith, G. M., and Armem, R. N.: Pulmonary Moniliasis Treated by Brilliant Green Aerosol, Ann. Int. Med. 43: 1302, 1955.
6. Levy, E. S., and Cohen, D. B.: Systemic Moniliasis Complicating Corticotropin Therapy, A.M.A. Arch. Int. Med. 95:118, 1955.

ATLANTA, GEORGIA

FOR

NEXT MEETING

NOVEMBER 16-19, 1959

MAKE PLANS NOW TO ATTEND!

Quinacrine in the Treatment of Discoid Lupus Erythematosus: A Five Year Follow-Up Survey — Results and Evaluation*

ROBERT N. BUCHANAN, JR., M.D., *Nashville, Tenn.*

This five year follow-up study in the treatment of discoid lupus with quinacrine confirms other reported studies of its value. Though not universally effective, it offers help in such a high percentage of cases as to make it a drug worthy of trial in these cases.

FIVE YEARS AGO, at the annual meeting of the Southern Medical Association, observations were presented on the effectiveness of quinacrine in the treatment of 32 patients with discoid lupus erythematosus.[1] It seems appropriate to restudy this group of patients 5 years later and evaluate the long-term effectiveness of quinacrine treatment. Such is the purpose of this report. No attempt is being made to study patients who have been treated by any other scheme of therapy including other antimalarial drugs.

Presented in tabular form is the 5 year follow-up status on the group in the original study (Tables 1 and 2). One patient (Case 5) was discarded from the series. She did not improve on treatment with quinacrine. Subsequent observation and study, including examination of a section of the skin, revealed findings not consistent with the diagnosis of lupus erythematosus. Therefore this patient is not included in the current report. The remainder who are not included could not be located. Additional information and their current status is not available through our records, letters addressed to the last known residence, efforts to locate the patients by telephone, or through inquiries directed to the referring physician when that information was available.

Classifying the results, the evaluation *excellent* means complete clearing of any sign of active inflammation. Residual scarring and variations in pigmentation were not regarded as signs of active disease.

The evaluation *good* means the patient responded favorably to quinacrine but healing was not complete and the process had become quiescent. These patients have required additional treatment with quinacrine or other similar drugs—frequently chloroquine. In this group the drugs have been helpful but have not produced a permanent cure.

In the group classified as *failure* there was either no benefit or negligible benefit from quinacrine given for a considerable period, or the drug had to be discontinued because of intolerance or complications. Therefore in this group of 25 patients the evaluation after 5 years is *excellent* in 7, *good* in 13 and *failure* in five.

One patient developed an extensive lichen planus-like eruption which forced stopping the drug. Others complained of nausea and diarrhea if the dose was large, but in no other instance was it necessary to discontinue the medication totally. No patients in the series developed systemic lupus after quinacrine was begun, although 3 had subacute systemic involvement prior to being treated with mepacrine.

During the earlier and more acute phase of the systemic disease these 3 patients were treated with cortisone. Later, after the disease had become stabilized, treatment was changed to quinacrine, and additional improvement was noted in all. However, in none of these has there been complete recovery. All 3 are classified in the category *good*.

The 3 patients with systemic disease were in the hospital during the more acute phase of the disease, while the remainder were

*Read before the Section on Dermatology and Syphilology, Southern Medical Association, Fifty-Second Annual Meeting, New Orleans, La., November 3-6, 1958.

TABLE 1

GROUP I. PATIENTS WITH CONSIDERABLE TREATMENT BEFORE THE USE OF QUINACRINE

Case	Age	Sex	Duration Years	Severity	Location	Previous Treatment	Quinacrine Schedule	Quinacrine Stopped and Result	Intolerance	Evaluation	Present Status	Additional Rx.	5 Yr. Evaluation
1	42	F	2-3 yrs.	Moderate	Forehead	Vitamin E, gold, crude liver	300 mg. x 7 200 mg. x 7 then 100 mg. daily for 6 mos.	Mild recurrence	None	Completely clear, excellent	Clear	Yes	Excellent
2	25	F	2 yrs.	Moderate	Cheeks, face	Bismuth, gold, cortisone ung. vitamin B_{12}	300 mg. x 7 200 mg. x 7 then 100 mg. daily for 8 mos.	Stopped, no relapse in 4-5 mos.	None	Completely clear, excellent	Clear	Yes	Good
3	35	M	16 yrs.	Moderate	Cheeks, face	Radium, x-ray, gold, cortisone ung. vitamin B_{12}	100 mg. x 7 200 mg. x 7 100 mg. daily	Did not clear, stopped treatment, no change	None	Unimproved	Better	Yes	Good
4	35	M	1-2 yrs.	Severe	Neck, about ears	Radium, x-ray, gold, cortisone ung. vitamin B_{12}	300 mg. x 7 200 mg. x 7 100 mg. x 30 300 mg. daily	Still on treatment	None	Improved, good	Better	Yes	Good
5	35	F	2 yrs.	Mild	Temples	X-ray, ointments	300 mg. x 7 200 mg. x 7 100 mg. daily	Stopped treatment, no change with L.E.	Biopsy not consistent		Discarded		
6	43	F	15-18 mos.	Severe	Face	Gold (worse), cortisone, I.V. ACTH, vitamin B_{12}	300 mg. x 7 200 mg. daily	Still under treatment	None	Definite improvement, good	Better	Yes	Good
7	42	M	About 4 yrs.	Moderate	Face	X-ray, gold, liver, B_{12}, improving	100 mg. daily later 100 mg. b.i.d.	Still under treatment	None	Good	Better	Yes	Good
8	42	M	4-5 yrs.	Moderate	Temples	Fulguration, mixed tocopherols, gold, improved	300 mg. x 7 200 mg. daily	No treatment for 4 mos.	None	Good	Clear	No	Excellent
9	63	F	4 yrs.	Mild	Tip of nose	X-ray, tocopherols, bismuth, gold, improved	300 mg. x 7 200 mg. x 7 100 mg. daily	Still on treatment	None	Not well, good	Clear	Yes	Excellent
10	40	M	Recurrence few mos.	Moderate	Face	Gold, 2 series previously None this time	300 mg. daily	Stopped only 12 das.	None	Clear, excellent	Better	Yes	Good
11	39	F	12-15 mos.	Extensive discoid	Face, neck, forearms, hands	Cortisone, vitamin B_{12}, cleared	Cortisone and quinacrine	Cleared	Abdominal pain, nausea	Good	Clear	Yes	Good
12	50	F	15-18 mos.	Moderate	Forehead, temples, scalp	Vitamin B_{12}, improvement	100 mg. t.i.d. x 7 100 mg. b.i.d. x 7 100 mg. daily	Apparently nearly well, stopped, relapse after 2 mos.	None	Improved, good	Clear	Yes	Excellent
13	54	M	? 12 ? 18 mos.	Severe purpura 1942; involvement of face, lips, 1951	Face	Mercury, lotions, salicylic acid, gold, hospitalization for I.V. ACTH, cortisone, viamin B_{12}, cortisone ung.	300 mg. x 7 200 mg. x 7 100 mg. daily	Stopped, recently was not well	None	Improved, good	Better	Yes	Good

TABLE 2

GROUP II. PATIENTS WITH LITTLE TREATMENT BEFORE THE USE OF QUINACRINE

Case	Age	Sex	Duration Years	Severity	Location	Previous Treatment	Quinacrine Schedule	Quinacrine Stopped and Result	Intolerance	Evaluation	Present Status	Additional Rx.	5 Yr. Evaluation
14	42	M	1 yr.	Mild	Face, neck	None	300 mg. x 7 200 mg. x 7 100 mg. daily	Improved, discontinued drug. Relapsed, resumed quinacrine	Diarrhea	Good			
15	12	M	Few mos.	Moderate albuminuria	Face, eyelid, region of ear	Vitamin B complex	300 mg. x 7 200 mg. x 7 then 100 mg. daily and vitamin E & B	No relapse 2 mos.	None	Excellent	Clear	Yes	Excellent
16	52	F	2 yrs.	Mild	Bridge of nose	Fulguration B.A.	200 mg. x 7 100 mg. daily	Treatment stopped 6 mos. No relapse	Nausea and Diarrhea	Excellent	Clear	No	Excellent
17		M	Few wks.	Mild	Face	None	300 mg. x 7 200 mg. x 7	Cleared, stopped Rx. and relapsed	None	Good			
18	43	M	1 yr.	Moderate	Side of face	None	300 mg. x 10 200 mg. daily	Improved, did not completely clear; stopped drug, relapsed	Pain in Back	Good	Better	No	Good
19	26	F	1 yr.	Moderate	Face, nose	None	300 mg. x 7 200 mg. x 7	Stopped drug, relapsed 2 mos.	Some nausea and diarrhea	Good	Better	Yes	Good
20	50	F	Several	Extensive discoid	Forearms, arms, neck	Ointments, vitamins	200 mg.	Still under treatment	None	Improved			
21	38	F	7-8 mos.	Moderate	Nose	None	300 mg.	Stopped 1 mo., no relapse	None	Clear, excellent	Clear	Yes	Excellent
22	62	M	Few mos.	Moderate	Sides of face	None	200 mg.	Treatment stopped because of rash	Rash	Unimproved	Better Slight L.E.	No	Poor
23	40	F	Few mos.	Mild	Nose, upper lip	None, ung.	200 mg. daily then 300 mg. daily	Still under treatment	None	Slight improvement	Unchanged	Yes	Poor
24	39	M	1 mo.	Moderate	Face, ear	None	300 mg. x 21 200 mg. x 28 then 100 mg. daily	Still under treatment	None	About well, excellent	Clear	No	Excellent
25	33	M	2-3 yrs.	Moderate	Sides of face	None	300 mg. x 7 200 mg. daily	Still under treatment	None	About well, excellent	Active L.E.	Yes	Poor
26	85	F	3 mos.	Severe	Face, neck	X-ray and local treatment	300 mg. x 14 200 mg. daily	Still under treatment	Some nausea	Great improvement, excellent			
27	40	M	2-3 yrs.	Moderate	Forehead, nose, cheeks	Various local treatments	300 mg. x 7 200 mg. daily	Stopped, remained status quo. Given chloroquine 6 wks. Back on quinacrine	None	Improved, good	Unchanged	Yes	Poor
28		F	4-5 mos.	Moderate	None	None	300 mg. x 7 200 mg. daily	Still on drug	None	Completely clear, excellent			
29	35	M	3-4 mos.	Moderate	Cheeks, nose, ear lobe	None	300 mg. x 7 200 mg. daily	Still under treatment	None	Improved, good	Better	Yes	Good
30	49	F	6 mos.	Mild	Lip, shoulder	Ointments, no benefit	200 mg. daily	Completely cleared, off drug 1 mo.	None	Cleared, excellent	Better	Yes	Good
31	29	M	9 mos.	Moderate	Face, neck, ears, scalp	None	300 mg. x 7 then 200 mg. daily	Still under treatment	None	Improving, good			
32	37	M	4 yrs.	Moderate	Jaws, neck	None	300 mg. x 7 200 mg. daily for 7 wks.	No relapse in 2 mos.	None	Cleared, excellent	Unchanged	Yes	Poor

treated without hospital care.

It is absolutely impossible to state accurately how much quinacrine has been taken. Some of these patients had neglected to return for follow-up evaluation until the present study was undertaken. All were able to obtain quinacrine by having the prescriptions refilled,—a fact which no doubt contributed to delinquency in follow-up observations. Several volunteered the statement that they would take the drug when active red lesions reappeared and would stop therapy when improvement followed.

No correlation could be noted between how extensive the lesions and how favorable the response. Of the failures, 3 had only a few small areas of discoid involvement.

The duration of the disease prior to quinacrine therapy seemed to have some effect on the outcome. Of the 12 patients in Series I, who had had the disease for months or years and who had had other accepted treatment prior to quinacrine treatment, all responded favorably and were rated either *excellent* 3 or *good* 9. In Series II, representing patients who had not had the disease for long periods and who had not had other recognized therapeutic regimens, all 5 *failures* were encountered.

Four of this series showed an *excellent* response and a like number were regarded as *good*. Perhaps this means that the natural course of the disease is toward final stabilization and that patients who have been troubled longer are more likely to be favorably influenced by effective drugs.

Two patients, cases 25 and 27, who showed an initial improvement to treatment, later relapsed and were not helped by quinacrine.

These results of 28% *excellent* response, 52% *good* and 20% *poor* are roughly similar to the observations of Christiansen and Nielsen[2] who reported upon 97 patients with discoid lupus; 27% showed an excellent result, 42% improved and 31% were unchanged or doubtful. In their series of 16 erythematous cases, 9 (56%) obtained an excellent result, 5 (31%) improved, and 2 (13%) were unchanged or doubtful. If these figures are combined to compare, therefore, with the series being reported today, the results are excellent in 31 (32%), good in 39 (40%), and ineffective in 28 per cent. Their follow-up period was for 2 to 3 years. Their final paragraph states, "After stopping treatment most of the patients were observed for about twelve months. The number of relapses during the period of observation was about 80 per cent. The frequent relapses seem to indicate that the effect of mepacrine is symptomatic rather than curative."

What can be learned from these observations? Can recommendation for the best dose schedule and duration of treatment be made? Is there any information as to the mechanism by which quinacrine is helpful in lupus erythematosus?

In Group I, in which the patients were originally placed together, because they had had discoid lupus for a considerable time prior to being treated with quinacrine, 3 of 12 (25%) obtained excellent results. Such a small group cannot be statistically significant. The question naturally arises, does the combination of quinacrine with other accepted treatment regimens offer added likelihood of success? I think it probably does. All in this group of 12 (case 5 has been taken out) had been refractory to other forms of treatment, which included vitamin E, the tocopherols, injections of liver extract, vitamin B_{12}, bismuth and gold. The results in the remaining 9 are classified as *good*. No one was classified as showing a *poor* response.

The 5 classified as *poor* occurred in Group II, in which treatment prior to administration of quinacrine was none or negligible. Case 22 is classified as *poor* because the patient developed a lichen planus-like eruption which forced interdiction of the drug. Nevertheless, the other 3 (Cases 23, 27 and 32) have been able to take the drug for long periods and in considerable amounts. The patients of cases 23 and 32 have not improved on a variety of therapeutic schemes which have included the use of other antimalarials and injections of heavy metals—bismuth and gold. However, the patient in case 27 improved considerably on weekly injections of gold sodium thiosulfate after he failed to yield to quinacrine.

Evidence is adequate and convincing that the drug is effective. Is there any information regarding the best dosage schedule and duration of treatment? The patient in case 11, who had subacute systemic lupus erythematosus and had been treated with cortisone, injections of liver extract and of B_{12}

prior to quinacrine therapy, volunteered the comment that quinacrine is the most effective drug which had been given. This patient, along with others, has found it necessary to repeat courses of treatment with quinacrine daily, bringing prompt improvement. She begins by taking 600 mg. of quinacrine daily, which she continues as long as she can tolerate this dose level; then the dose is dropped because of gastrointestinal symptoms. Other patients have commented that large doses, if they can be tolerated, bring about prompt and more impressive improvement. A program of vigorous treatment is consonant with the recommendation of Howell[3] in regard to the dose of chloroquine in treating the same problem.

Since the majority, indeed, almost all of the patients who were benefited by treatment with quinacrine required additional courses, it is apparent that short periods of treatment are not ideal. Therefore, treatment should be continued for several months (I believe for at least 6 months) after all signs of active disease have disappeared.

From this study no findings reveal any information about the mechanism by which quinacrine is helpful. Herrmann and Miller[4] have shown that the drug is deposited in the skin where it produces a fluorescence when examined under filtered ultra-violet light, but this does not reveal its mode of action upon the lupus. Harvey and Cochrane,[5] quoting Currie, state that joint symptoms are not improved by quinacrine. This statement is at variance with the reports of several observers. Martin, Cominole and Clark[6] found the adrenal glands of dogs receiving 200 mg. of Atabrine per kilogram per day appeared essentially normal on necropsy.

This report is at variance with the observations of Nagy and associates[7] who, in an effort to understand the action of Atabrine, did animal experiments in which cats given the drug during a pre-experiment period were able to survive doses of histamine fatal for animals not pre-treated with Atabrine. Animals treated with Atabrine showed considerably (nearly 30%) increased secretion of 17-ketosteroids and markedly heavier adrenals. There was hypertrophy of the adrenal cortex. From their observations they draw the following conclusions:

(1) Atabrine has an antihistaminic action;

(2) Its influence is, however, not to be explained by strengthening of the antihistaminase action;

(3) Animals pretreated with Atabrine show hypertrophy of the adrenal cortex with increased lipoid production which supports the earlier suggestion of the authors that the adrenal cortex plays a part in the mechanism of the action of Atabrine. There are, however, still further factors to be investigated besides the antihistamine effect.

Shelley and Arthur[8] concluded that *chloroquine* and not quinacrine failed to stimulate the adrenal cortex as evaluated by steroid assays, eosinophil and white counts. They conclude that the therapeutic mechanism of the action of chloroquine does not involve the adrenal cortex. So its mode of action has not yet been definitely established, and published reports concerning its possible mode of action are conflicting.

Summary

Five years ago it appeared fair to state that, "It seems generally agreed that quinacrine is effective in from 60 to 90% of those cases treated."[1] However quinacrine, like many others, has not turned out to be all it seemed in the first blush of introduction. Quinacrine is helpful in about three-fourths of the patients. In about one-fifth it is either not tolerated or is ineffective, and in only about one-fourth has it proved to be curative. Christiansen and Nielsen[2] noted that about 80% experienced relapses. In only 3 of this series (12%) has it been immediately effective (Cases 8, 16 and 24) and no relapses have occurred.

The problem of effective treatment of lupus erythematosus remains unsolved.

Our conclusions of 5 years ago were:

"From various reports, including ours, it seems generally agreed that quinacrine is effective in from 60 to 90% of those cases treated. Its mode of action is not known. Undesirable reactions do occur, but the majority of these are not severe or serious. If customary care is observed and warning signals heeded, serious difficulties should be avoided.

"It is simple to administer, and it is comparatively cheap.

"Apparently it is as effective as, if not the most effective of, all the drugs which have been used.

"Further observation and study are required before the most effective dose schedule and duration of treatment is known."

These previous conclusions should now be modified to state that:

(1) The drug is effective but that relapses are frequent;

(2) We know that there are other similar drugs available and which are somewhat preferable;

(3) Relapses often yield to repeated courses of treatment; and

(4) Treatment should be energetic and prolonged if permanent benefit is to be effected.

References

1. Buchanan, Robert N., Jr., King, Howard, and Hamilton, C. M.: Quinacrine in Discoid Lupus Erythematosus. The Present Day Status, South. M. J. 47:678, 1954.
2. Christiansen, Jorgen V., and Nielsen, Johs. P.: Treatment of Lupus Erythematosus with Mepacrine, Brit. J. Dermat. 68:73, 1956.
3. Howell, R. G.: Chloroquine In Discoid Lupus Erythematosus, Tr. The St. John Hosp. Dermatological Soc. 39:48, 1957.
4. Herrmann, F., and Miller, O. B.: Pharmacologic and Pathogenic Effects of Mepacrine Chloride (Atabrine) on Human Skin, Acta dermat.-venereol. 32:304, 1952.
5. Harvey, George, and Cochrane, Thomas: Treatment of Lupus Erythematosus with Mepacrine (Atabrine), J. Invest. Dermat. 21:99, 1953.
6. Martin, S. J., Cominole, B., and Clark, B. B.: Chronic Oral Administration of Atabrine, J. Pharmacol. & Exper. Therap. 65:156, 1939.
7. Nagy, E., Kocsár, L., Jókay, I., Hadhazy, Cs., and Tuza, K.: New Data on Mechanism of Action of Atabrine, Dermatologica 115:143, 1957.
8. Shelley, Walter B., and Arthur, Robert P.: The Failure of Chloroquine to Stimulate the Human Adrenal Cortex, J. Invest. Dermat. 31:109, 1958.

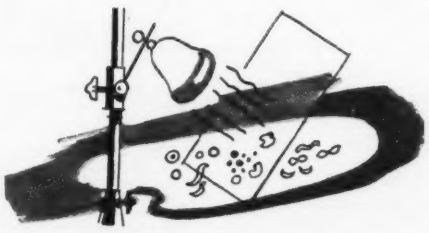
Discussion (Abstract)

Dr. J. Richard Allison, Jr., Columbia, S. C. I would like to congratulate Dr. Buchanan on his excellent and most worthwhile paper. Too often most of us jump on the bandwagon of new treatment methods without proper plans for any real evaluation and long-term follow-up. I only hope Dr. Buchanan will be able to follow this group for another five years and that his example will stimulate more of us toward similar evaluations and follow-ups in this and other problems. Another example of the value of evaluation studies was the recent paper of Drs. Epstein and Allington (A.M.A. Arch. Dermat. 76:400, 1957) who evaluated the treatment of herpes zoster in the past 26 years and who concluded that no type of treatment shortened the course of the disease—a point one of them did not feel was true until the evaluation was made, and a point to all of us to re-evaluate our treatment programs as they did and as Dr. Buchanan has done here so well.

In Dr. Buchanan's series those patients who had had the disease longer seemed to clear better, there being no failures in this group and the author suggested this might be due to a "final stabilization." However, Crissey and Murray (A.M.A. Arch. Dermat. 74:69, 1956) in their series considered statistically, could find no correlation between the duration of the disease before treatment and its response to either gold or chloroquine treatment. They concluded that there was no significant difference in the proportion of cases that responded to these drugs and although chloroquine gave a quicker response it was subject to quicker relapses than gold therapy. For this reason, we have been treating our patients initially with chloroquine as it gives a quicker response, but fearing relapses and feeling that the combined therapy is better, we then follow with a course of gold before trying to establish a final maintenance dose of chloroquine or discontinuing treatment.

As to the mode of action of this group of drugs, Epstein, Forsham and Friedman in a recent paper before the Society of Investigative Dermatology noted the presence of more free corticoids in the plasma (but not in the urine) of subjects on chloroquine. They felt that these findings suggested that chloroquine impaired the hepatic reduction and conjugation of the free 17-hydroxycorticoids from the plasma. This is certainly an interesting finding and hypothesis, as a possible mechanism of action, and bears further investigation and study.

It has been a privilege and a stimulus to discuss Dr. Buchanan's paper and again I wish to thank him for his presentation.



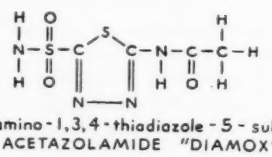
A Note on Hydrochlorothiazide as A Therapeutic Agent

TOM D. SPIES, M.D., WILLIAM NIEDERMEIER, M.S., and ROBERT E. STONE, M.D.,† *Birmingham, Ala.*

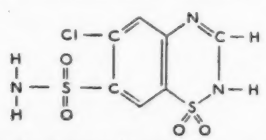
FOR YEARS we, as well as many others, have been effecting changes in the body chemistry of edematous persons, often with the result that much of the accumulation of fluid was excreted from the body. The effectiveness of acetazolamide (Diamox) and chlorothiazide (Diuril) has been observed by us and others. Sometime ago a new compound hydrochlorothiazide (HYDRODIURIL) was supplied to us by Dr. Augustus Gibson of Merck & Co., Inc. As can be seen in figure 1, hydrochlorothiazide differs slightly from chlorothiazide in chemical structure. We were interested in learning if this change in structure might have an important therapeutic effect. We have found this to be the case and is the basis of this brief report.

Since the effect of hydrochlorothiazide was unknown, we first administered it in very small amounts and soon found it had no ill effect on physiologic function. We then gave it to a few selected patients with edema. Figure 2 shows the changes in a representative patient following its administration. This patient was arbitrarily selected.

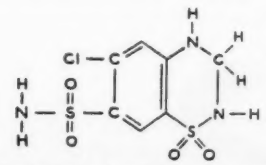
FIG. 1



2-acetylamino-1,3,4-thiadiazole-5-sulfonamide
ACETAZOLAMIDE "DIAMOX"

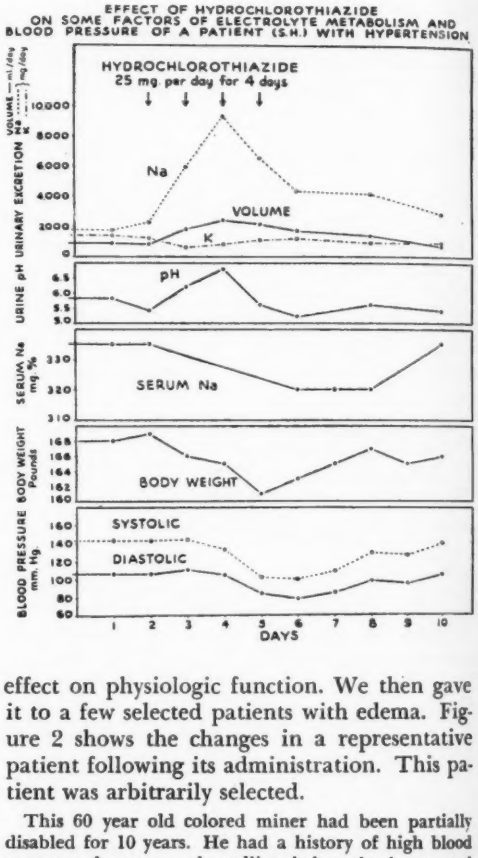


6-chloro-7-sulfamyl-1,2,4-benzo-thiadiazine-1,1-dioxide
CHLOROTHIAZIDE "DIURIL"



6-chloro-7-sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide
HYDROCHLOROTHIAZIDE "HYDRO DIURIL"

FIG. 2



This 60 year old colored miner had been partially disabled for 10 years. He had a history of high blood pressure, dyspnea, and swelling below the knees, and was said to have silicosis and an enlarged heart.

Physical examination showed swelling below the knees. The heart was enlarged.

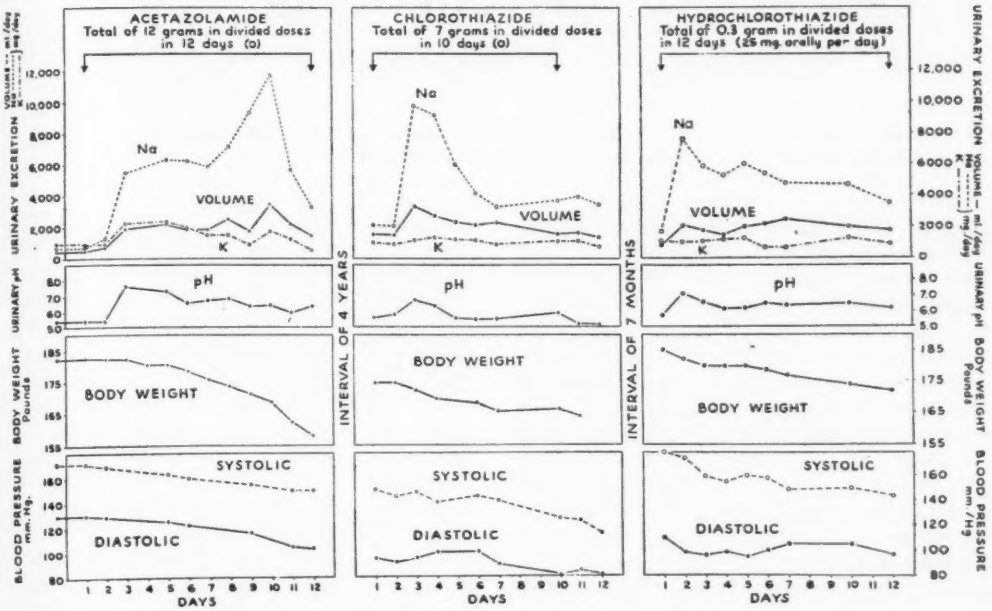
†From the Department of Nutrition and Metabolism, Northwestern University Medical School, Chicago, Ill. Studies in Nutrition at the Nutrition Clinic, Hillman Hospital, Birmingham, Ala.

This study was made possible by grants from the Republic Steel Educational and Charitable Trust, the Procter and Gamble Fund, and the Birmingham Citizens Committee Fund.

(Dr. Ramón M. Suárez, Sr., Hospital Mimiya, Santurce, Puerto Rico, and one of the authors (T.D.S.) are studying this compound in Puerto Rico.)

FIG. 3

EFFECT OF ACETAZOLAMIDE (DIAMOX), OF CHLOROTHIAZIDE (DIURIL) AND OF HYDROCHLOROTHIAZIDE (HYDRODIURIL) ON SOME FACTORS OF ELECTROLYTE METABOLISM AND BLOOD PRESSURE OF A PATIENT (U.B.) WITH CONGESTIVE HEART FAILURE



In the B.P. determinations, the systolic ranged from 140 and 160 mm. Hg., the diastolic from 110 and 116 mm. Hg. His body weight on admission was 169 pounds.

A diagnosis of silicosis was made from the physical examination, history, and x-ray findings.

He was given 25 mg. of hydrochlorothiazide daily for 4 days. The output of urine increased, and there was a decrease in blood pressure and in the swelling of his legs. He lost 5 pounds of weight in two days. This improvement has been maintained for a period of 35 days on a dosage of 25 mg. daily. The B.P., which became normal on the fifth day of therapy, has remained within normal limits.

At this dosage level hydrochlorothiazide is as effective as was 250 mg. of chlorothiazide administered on other occasions to this patient. His response to both drugs seems to be parallel in all ways.

We have a considerable number of patients who have been relieved by acetazolamide and the same patients have also been relieved by chlorothiazide. We wanted to see if these patients would be relieved by hydrochlorothiazide under the same conditions. As can be seen in figure 3, hydrochlorothiazide is considerably more potent per unit of weight than either acetazolamide or chlorothiazide in producing diuresis and in relieving some of the symptoms of hypertension. The new drug when given in a relatively small amount, one-tenth or even less than the dose of chlorothiazide, produced increased excretion of sodium and water, a decrease in body weight, and a tendency toward lowering abnormally high systemic blood pressure.

These observations suggest that hydrochlorothiazide is an extremely effective therapeutic agent and will find a useful place in clinical medicine.

Citrated Calcium Carbimide in the Treatment of the Alcoholic*

MERRITT W. FOSTER, JR., M.D.,† *Richmond, Va.*

The author describes the use of a substance, whose effects had been recognized a half century before, as an adjunct in the treatment of alcoholism.

In 1948, Hald, Jacobsen and Larsen[1] discovered that the drug known as disulfiram would sensitize an individual so that the ingestion of alcohol would become intolerant. Since that time this drug better known by its trade name, Antabuse, has enjoyed a rather wide popularity as an adjunct in the treatment of alcoholics. Early papers reporting the reaction to alcohol in the individual sensitized with Antabuse described a similar syndrome occurring in France among workers in the carbide plants. This symptom complex was popularly known as the "mal rouge," and consisted of flushing of the face, shortness of breath, and palpitation. It occurred only in those workers who drank alcoholic beverages. As early as 1914 we have a report by Koelsch that calcium carbimide would cause a hypersensitivity to alcohol as noted in workers exposed to this compound. The reaction described by this author appears grossly identical with the symptom complex just described, as well as with the classical Antabuse challenge.

Because the continuous ingestion of Antabuse frequently caused unpleasant side effects, Ferguson,[2] at the University of Toronto, began a series of experiments with carbimide compounds, since these substances were known to have remarkably few toxic effects apart from the disagreeable reactions with alcoholic beverages. He was able to develop a combination of calcium carbimide and citric acid which most nearly fulfilled the desired aim. This substance currently produced under the trade name of Temposil (although not yet on the open market) has been undergoing clinical trials[3] both in Canada and the United States since its development in 1956.

The pharmacologic effectiveness of citrated calcium carbimide proceeds in much the same manner as that with disulfiram. The oxidation of alcohol is blocked at the aldehyde level causing a marked rise in blood acetaldehyde. In addition, receptors in the individual's cardiovascular apparatus apparently become abnormally reactive to acetaldehyde. The combination of these two forces causes the well known clinical picture of flushing of the face, conjunctival injection, palpitation, dyspnea, tachycardia, and in more severe reactions a fall in blood pressure. Generally speaking, however, the clinical reaction to alcohol in the sensitized individual is somewhat milder with this new drug than with Antabuse.[4] Another prominent difference between the two drugs is that alcohol sensitivity with Antabuse is slowly acquired over a period of 4 to 5 days and is slowly relinquished, lasting an equal or slightly longer time, after the drug has been discontinued. With the carbimide however, the individual is sensitized within 2 hours following the ingestion of the drug, but the sensitivity to alcohol lasts only from about 8 to 15 hours. A more important and useful dissimilarity lies in the side effects which may occur when the drug is taken alone without the addition of alcohol. With Antabuse these side effects may be rather marked. They include nausea and other gastrointestinal symptoms, impotence, marked drowsiness and, on rare occasions in our experience, even toxic psychosis. With Temposil they are usually nonexistent, or at most very mild.

Our procedure in the use of the carbimide begins with the admission of all patients to the hospital. Here they can be given a period of enforced abstinence from alcohol and treated when necessary for the acute effects of intoxication. This is followed by a complete clinical study with particular attention given

*Read before the Section on Neurology and Psychiatry, Southern Medical Association, Fifty-Second Annual Meeting, New Orleans, La., November 3-6, 1958.

†From the Department of Psychiatry, Medical College of Virginia, Richmond, Va.

to the liver function tests. If these studies are normal and the BSP retention is less than 15%, the patient is offered the opportunity of taking the drug. If he elects to use this medication to assist him in maintaining his sobriety, a daily dose of 50 mg. is begun. On the second day of treatment he is given the alcohol challenge which consists of a test dose of 50 cc. of 86 proof whiskey administered two hours after the drug. We have found that this amount of alcohol is sufficient to produce a very definite although not an overwhelming reaction in the patient. On the day following the test reaction or challenge and providing no further symptoms are present, the patient is discharged from the hospital to be followed in the office. He is charged then with the responsibility of continuing his daily dose of 50 mg. of the citrated calcium carbimide.

The relative safety of Temposil administration is becoming more and more apparent. Approximately 753 patients have been given this drug as of the present time.[5] They range in age from 21 to 72 years. Of the 753 patients treated so far, one or more side effects have been reported in only 38. In these 38 the most common side effect was mild drowsiness which is actually thought by some to be beneficial in the treatment of alcoholism. One patient is known to have taken 34 tablets at one time without benefit of medical attention for approximately 10 hours. In spite of this he showed a normal pulse, blood pressure, and respiratory rate. The only side effects noted were nausea, anorexia, and mild drowsiness which lasted for 2 days. A transient rise in the white blood count has been reported, but this is an uncommon finding, and bone marrow studies in these cases have been universally negative. All of the usual liver function studies have remained unchanged with administration of the carbimide. Some of the patients in our series have received daily doses of 50 mg. for as long as 24 months without any adverse side effects. This has been particularly useful since almost all of these cases were given Temposil because they did not tolerate Antabuse. This was usually due to marked drowsiness, severe gastrointestinal symptoms with nausea and/or diarrhea, and in two cases due to the development of a toxic psychosis. The alcohol challenge with Temposil is definitely milder than that with Antabuse. In only one of our series of cases in which citrated calcium carbimide was used has the blood pressure fallen below 110 systolic. In this case the decline reached a reading of 80 with a diastolic pressure of 40. Otherwise this particular reaction was not threatening. The carbimide alcohol reaction can be terminated satisfactorily in our experience with doses of ascorbic acid up to 2 Gm. intravenously. Others have reported similar results with antihistaminics and oxygen.

In spite of the relative safety of this drug, we have believed the short period of pharmacologic effect following ingestion of the drug is not as practical and, therefore, less effective therapeutically than Antabuse with its more prolonged period of action. This would seem to outweigh the possible side effects of Antabuse plus the somewhat more severe alcohol challenge with Antabuse. We feel, therefore, for routine usage in a carefully controlled situation that disulfiram is preferable, but that the carbimide at the present time can be extremely helpful in patients who do not tolerate the former. If studies currently under way are successful, a variation of Temposil may be produced which will give a more sustained period of sensitivity. In such an altered form this drug may well prove ultimately to be superior.

References

1. Hald, J., Jacobsen, E., and Larsen, V.: The Sensitizing Effect of Tetraethylthiuram-disulfide (Antabuse) to Ethyl Alcohol. Acta pharmacol. et toxical. 4:285, 1948.
2. Ferguson, J. K. W.: A New Drug for the Treatment of Alcoholism, Canad. M.A.J. 74:793, 1956.
3. Armstrong, J. P.: The Protective Drugs in the Treatment of Alcoholism, Canad. M.A.J. 77:228, 1957.
4. Smith, J. A.: The Use of Citrated Calcium Carbimide in Treatment of Chronic Alcoholism, J.A.M.A. 165:17, 1957.
5. Cahoon, R. P.: Personal Communication.

Discussion (Abstract)

Dr. Jackson A. Smith, Omaha, Nebr. We have used citrated calcium carbimide in 138 alcoholics during the past 2 years. We do not share Dr. Foster's concern over the rapid rate of excretion of this product as compared to disulfiram, since, in our own experience, the alcoholic who plans to drink will usually wait the few extra days necessary to excrete the disulfiram as readily as he would wait one day if he were taking calcium carbimide.

Occasionally, a patient requires more than 50 mg. daily to produce a reaction, but this, in our experience, has been the exception. The advantages possessed by Temposil, in not producing marked cardiovascular reactions after the patient drinks, and the lack of side effects from taking the drug as compared to disulfiram, would appear to make it the more desirable of the two methods of treatment.

I have enjoyed hearing Dr. Foster's report, and so far as I know, this is the first effort to bring together the results of various investigators who have tested this preparation.

Pancreatitis: A Twelve Year Review*

BENJAMIN B. WEISIGER, M.D.,† *Richmond, Va.*

Experience has shown that pancreatitis may have lesser clinical manifestations than recognized in the past. Furthermore, causes other than alcohol must be suspected and searched out.

THE PAST SEVERAL YEARS have witnessed startling changes in our concepts of pancreatitis. This has been evident not only in the discovery of increasingly varied causes, but also in our access to increasingly accurate diagnostic aids.[1,2] The cases of pancreatitis admitted during the past 12 years to the McGuire Veterans Administration Hospital, Richmond, Virginia, have been reviewed in the light of these recent developments and it is these findings which are the subject of this presentation. After eliminating those cases whose diagnosis was questionable, 103 patients with pancreatitis remained. Only the first 100 of these were reviewed for the purposes of ease of study. There were 222 admissions in this group of patients.

Incidence

Customarily, pancreatitis is divided into types, such as acute interstitial, acute hemorrhagic, and chronic relapsing. Many believe these are probably all variants of the same process, and that chronic relapsing pancreatitis may follow either an interstitial or an acute hemorrhagic episode. The majority of our cases were of the chronic relapsing type (Table 1). This emphasizes the need for considering this diagnosis even in mild varieties of abdominal pain. The greatest percentage of deaths occurred in the acute hemorrhagic cases, as expected, although a number occurred with repeated episodes of chronic relapsing pancreatitis.[3] Due to the type of hospital and its location, the patients were all male with 59% white and 41% Negro. The vast majority of cases had their onset in the fourth decade with incidence in the third, fifth and sixth decades, being approximately half that in the fourth (Fig. 1). We were unable to detect any familial incidence in our cases, though this has been reported by others.[4]

TABLE 1

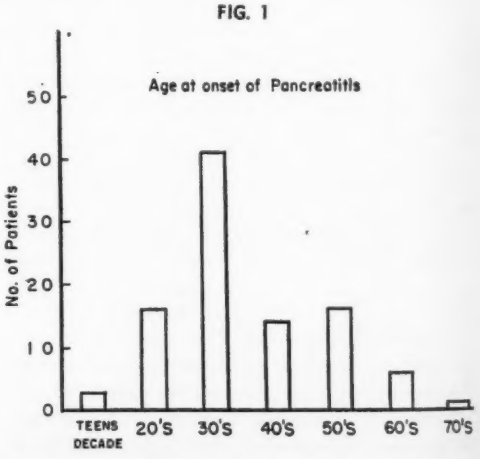
TYPES OF PANCREATITIS (100 PATIENTS)

Type	*Number of Patients*	*Number Deaths*
Acute interstitial	27	2
Acute hemorrhagic	6	4
Chronic relapsing	53	6
Acute interstitial followed by chronic relapsing	11	0
Acute hemorrhagic followed by chronic relapsing	3	1
Totals	100	13

Etiology

Over the past 50 years the chief theories of etiology have proposed obstruction to the pancreatic duct.[5-7] This has been attributed to edema of the ampulla of Vater with spasm of the sphincter of Oddi, or to biliary calculi in the presence of a common channel, with or

FIG. 1



The peak age of onset is in the fourth decade with that in other decades being about half as great.

*Read before the Section on Surgery, Southern Medical Association, Fifty-Second Annual Meeting, New Orleans, La., November 5-6, 1958.

†From the Gastrointestinal Section of the Medical Service, McGuire Veterans Administration Hospital, Richmond, Va.

TABLE 2

ETIOLOGIC FACTORS

1. Alcohol
2. Gallbladder disease
3. Other forms of obstruction
   - Pancreatic carcinoma
   - Ductal metaplasia (steroids)
   - Duodenal lesions (ulcer, polyp, diverticulum)
   - Ascaris
   - Congenital pancreatic duct abnormalities
4. Metabolic disturbances
   - Hyperlipemia
   - Hereditary pancreatitis
   - Diabetes
   - Malnutrition (Kwashiorkor)
   - Pregnancy
   - Hemochromatosis
   - Hyperparathyroidism
5. Trauma
6. Infection (specific diseases, extension from abdominal foci)
7. Vascular disease (arteriosclerosis, collagen diseases)
8. Allergy

without reflux of bile into the pancreatic duct. It has been shown that these factors are particularly active in the presence of an actively secreting gland following a large meal or intake of alcohol. Table 2 indicates the wide variety of causes of pancreatitis proposed in the last several years. Obviously, many of these are rare. Table 3 shows our experience with 100 consecutive cases at McGuire Hospital. In this group 73% were attributed to alcohol, 12% to gallbladder disease, 5% to vascular disease and 10% to various miscellaneous causes. The high proportion of alcoholic cases is probably due to the sex and social status of the hospital population, and the small incidence of gallbladder disease is due to the absence of women from the series. Though it has been theorized that vascular disease plays a part in all cases of pancreatitis, we were able to establish it as a primary cause in only 5 cases. Hepatitis, inflammation of a duodenal diverticulum, hyperparathyroidism, hyperlipemia, and two cases of unknown cause make up the rest of the group.

Essential hyperlipemia has been found by a number of authors to result in pancreatitis.[8] It is characterized by high serum lipids, especially neutral fat, but also cholesterol and

TABLE 3

ETIOLOGY IN 100 CASES OF PANCREATITIS

Etiology	*Number*
Alcohol	73
Gallbladder disease	12
Vascular disease	5
Miscellaneous*	10

*Hepatitis, duodenal diverticulum, hyperparathyroidism, hyperlipemia and unknown.

phospholipids. We were able to find only one case exhibiting this abnormality among all our patients tested. Hyperparathyroidism has been recently emphasized by Cope and others[9] as a cause of pancreatitis. We had only one case with this disease. Calcium and phosphorus determinations were done on repeated admissions on most of these patients. The large majority remained within the normal range throughout their hospital stay.

Clinical Course and Complications

The clinical course was relatively benign in most patients. The majority were febrile with an average peak fever for the entire 100 patients of 100.9°, and an average total duration of fever of 6 days. Pain occurred in the abdomen without radiation in over 50 per cent. It radiated to the back in 35%, and in most patients subsided rapidly on standard medical management. Complications did not appear to increase with the duration of the disease (Table 4). The great preponderance of complications occurred within the first 5 years of the disease and frequently occurred with the first attack. There were 13 pseudocysts, 17 cases of calcification, 13 frank diabetics, and 4 cases with gross steatorrhea. Balance studies would have undoubtedly revealed more cases of steatorrhea. There were 13 deaths in the entire series (Table 5). The majority of these occurred after repeated attacks and in patients with other diseases serious enough to cause mortality in themselves. In at least 3 of these death was apparently due to the other dis-

TABLE 4

DURATION OF PANCREATITIS PRIOR TO ONSET OF COMPLICATIONS

Complication	*Duration of Disease—Number of Patients*			*Totals*
	Less than 1 year	*1 to 5 years*	*More than 5 years*	
Pseudocyst	7	5	1	13%
Calcification	8	4	5	17%
Diabetes	7	3	3	13%
Steatorrhea	0	2	2	4%

TABLE 5

FINDINGS IN 13 FATAL CASES OF PANCREATITIS

Case	*Age*	*Type Case*	*Pancreatic Complications*	*Other Diseases*	*Alcohol*	*Duration of Disease*	*Surgery*
1	45	Chronic relapsing	Pseudocyst, calcification	Fatty liver	Yes	3 years	Cyst drained (another adm.)
2	54	Acute hemorrhagic	No	Cirrhosis, cholelithiasis	Yes	1st attack	No
3	52	Chronic relapsing	No	Fatty liver, thrombophlebitis	Yes	3 months	No
4	48	Chronic relapsing	Calcification	GI hemorrhage	Yes	2 years	Explored
5	30	Acute hemorrhagic	No	Hepatitis	No	1st attack	No
6	49	Chronic relapsing	Pseudocyst, calcification	Gastric ulcer	Yes	11 years	Marsup. cyst (another adm.)
7	29	Acute interstitial	No	Fatty liver	Yes	1st attack	Explored this adm.
8	29	Chronic relapsing	No	Fatty liver	Yes	Unknown	Pelvic abscess drained
9	44	Acute hemorrhagic	No	Gout, cirrhosis	Yes	1st attack	No
10	44	Chronic relapsing	Calcification, diabetes	Gas gangrene, syphilis	Yes	Unknown	No
11	56	Chronic relapsing	Calcification	Myocarditis, nephrosclerosis, duodenal ulcer	No	8 months	No
12	62	Acute interstitial	No	Arteriosclerosis pulmonary T.B.	No	1st attack	No
13	39	Acute hemorrhagic	No	Hypertensive cardiovascular disease, nephrosclerosis	No	1st attack	No

eases rather than to the pancreatitis. Only three of the patients were explored surgically during their final admission.

Diagnosis

Serum amylase. The serum amylase was the best method for the diagnosis of an acute episode. Initial determinations of serum amylase for 221 admissions to the hospital are tabulated (Table 6). The amylase in proven cases of pancreatitis was not always in the diagnostic range on admission, but at times rose later. After repeated attacks the amylase often failed to rise to abnormal levels. (The normal level by the method used was 20 to 40 units, with anything over 60 being highly significant.) Slightly more than half were in the diagnostic range initially on all admissions. However, a number of these had been previously diagnosed as pancreatitis.

Glucose. Of much help in the diagnosis of acute episode was the blood sugar determination. There was a 58% incidence of abnormality of glucose metabolism, implying edema or destruction of the islets of Langerhans (Table 7). These abnormalities varied from a positive diabetic glucose tolerance curve to a few cases of frank diabetes.

Miscellaneous. The majority of cases had some elevation of white blood count, the mean count being 11,390. Liver function tests were of little help in diagnosis except in the presence of frank jaundice, which was usually due to hepatitis, cirrhosis, or biliary calculi.

TABLE 6

INITIAL SERUM AMYLASE VALUES ON 221 ADMISSIONS FOR PANCREATITIS

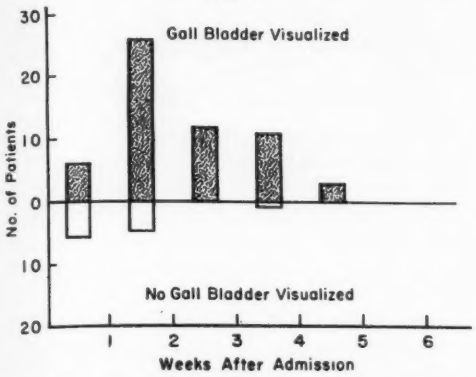
Range	*Number of Admissions*
Less than 20 units	12
20 to 40 units	48
41 to 60 units	43
Over 60 units	111
Not checked	1

TABLE 7

GLUCOSE METABOLISM—SEVEREST ABNORMALITY ON ANY ADMISSION

Abnormality	*Number of Patients*
Diabetes	13
Hyperglycemia	30
Diabetic glucose tolerance	15
Total	58
Normal	34
Not checked	9

FIG. 2



The large majority of patients without primary cholecystic disease had normal cholecystograms, if these were done more than one week after admission.

Alkaline phosphatase was rarely elevated in the absence of these complications.

X-ray. The x-ray was helpful in several ways. The barium meal suggested pancreatic disease by the presence of calcification, retroperitoneal mass, or enlargement of the pancreatic head in 48 cases. Plain films of the abdomen revealed a localized ileus with a so-called "sentinel loop" 28 times. Of even greater help was the use of the cholecystogram in ruling out gallbladder disease in alcoholic patients (Fig. 2). There has been controversy regarding the meaning of nonvisualized gallbladder in pancreatitis. The large majority of these were visualized after the first week, providing no primary gallbladder disease was present. At times, however, it was necessary to wait 6 to 8 weeks and re-examine the gallbladder by the x-ray to rule out biliary tract disease. All examinations were successful at the end of this time unless cholecystic disease was present. This may be so because of a temporary chemical cholecystitis due to reflux of pancreatic juice as has been suggested by others.[10] Four of our alcoholic patients had cholelithiasis as well.

Secretin test. The intravenous secretin test has been useful in diagnosing chronic or quiescent cases. This method measures the duodenal volume, amylase, bicarbonate, and bicarbonate concentration after stimulation of the pancreas with this hormone. These are measured by means of a double-lumen tube with constant suction, aspirating separately the stomach and duodenal contents. Peak values are expected within the first 40 minutes after the injection of secretin (Table 8). The drop in values from normal levels occurred in the majority of patients within the first 5 years of the disease. If the duration of the disease was less than one year the values were essentially normal. We also found, as noted by Dreiling,[11] Sun[12] and others, that after secretin the serum amylase tended to rise in the presence of chronic obstruction to the pancreatic duct.

Surgical Treatment

Though medical management has undergone few changes, a number of surgical procedures have been advocated for correction of pancreatitis. Surgical treatment was rather limited in this series and perhaps this is a result of a too conservative attitude on our part. A number of procedures were done with the majority of patients having recurrences of their symptoms, some as soon as 6 weeks after the operation (Table 9). Obviously, the num-

TABLE 8

RESULTS OF SECRETIN TESTS IN PANCREATITIS*

	Minimum Normal Values	*Less Than 1 Year in Duration*	*1 to 5 Years in Duration*	*Over 5 Years in Duration*	*Total Number of Tests*
		Mean	*Mean*	*Mean*	
Duodenal volume (cc.)	90	123.1	68.2	86.5	36
Duodenal amylase (Gm.)	29	78.5	49.5	62.2	37
Duodenal bicarbonate (mEq.)	10	11	5.8	3.9	26
Duodenal bicarbonate concentration (mEq./L.)	90	87.5	72.5	51.4	26

*Findings are expressed in relation to the duration of the disease. Values represent the mean figure obtained in 40 minute specimens after I.V. secretin (1 unit per Kg. of body weight).

TABLE 9

SURGICAL PROCEDURES IN PANCREATITIS

Procedure	*Number Done*	*Number with Recurrences*	*Interval Before Recurrence*	*Did Not Recur*
Splanchnicectomy	5	4	2 to 6 mos.	1
Marsupialization of pseudocyst	9	6	2 mos. to 3 yrs.	3
Cholecystectomy	10	7	2 mos. to 15 yrs.	3
Exploration	10	7	4 mos. to 10 yrs.	3*
Choledochostomy	4	2	2 to 8 mos.	2
Sphincterotomy	2	1	2 yrs.	1
Partial pancreatectomy	2	0		2
Cholecystoduodenostomy	1	0		1

*One death.

ber is too small to justify any conclusions but possibly may justify our conservative attitude in the past. I think everyone will agree that the ideal operation for pancreatitis has not been devised, as witness the many procedures advocated.

Summary

In the past 10 to 12 years we have altered our thinking regarding pancreatitis. Where formerly we only suspected severe board-like abdomens associated with shock, we now suspect everyone with a mild abdominal pain particularly when it is associated with the use of alcohol. Numbers of papers over this period of time have noted the varied causes for this disease and have stimulated us to look for etiologies which were not even suspected 10 years ago. The weakest point in management of pancreatitis still lies in its ultimate theory.

References

1. Richman, A.: Acute Pancreatitis, Am. J. Med. 21:246, 1956.
2. Gross, J. B., and Comfort, M. W.: Chronic Pancreatitis, Am. J. Med. 21:596, 1956.
3. Thal, A. P., Perry, J. F., Jr., and Egner, W.: A Clinical and Morphologic Study of Forty-two Cases of Fatal Acute Pancreatitis, Surg. Gynec. & Obst. 105:191, 1957.
4. Gross, J. B., and Comfort, M. W.: Hereditary Pancreatitis, Gastroenterology 32:829, 1957.
5. Opie, E. L.: The Causes and Varieties of Chronic Interstitial Pancreatitis, Am. J. M. Sc. 123:845, 1902.
6. Menguy, R. B., Hallenbeck, G. A., Bollman, J. L., and Grindlay, J. H.: Ductal and Vascular Factors in the Etiology of Experimentally Induced Acute Pancreatitis, A.M.A. Arch. Surg. 74:881, 1957.
7. Elliott, D. W., Williams, R. D., and Zollinger, R. M.: Alterations in the Pancreatic Resistance to Bile in the Pathogenesis of Acute Pancreatitis, Ann. Surg. 146:669, 1957.
8. Klatskin, G., and Gordon, M.: Relationship Between Relapsing Pancreatitis and Essential Hyperlipemia, Am. J. Med. 12:3, 1953.
9. Cope, O., Culver, P. J., Mixter, C. G., Jr., and Nardi, G. L.: Pancreatitis, a Diagnostic Clue to Hyperparathyroidism, Ann. Surg. 145:857, 1957.
10. Najarian, J. S., Hine, D. E., Whitrock, R. M., and McCorkle, H. J.: Effect of Pancreatic Secretions on the Gallbladder, A.M.A. Arch. Surg. 74:890, 1957.
11. Dreiling, D. A., and Janowitz, H. D.: Exocrine Pancreatic Function, Am. J. Med. 21:98, 1956.
12. Sun, D. C. H., and Shay, H.: Value of Combined Study of Serum Enzymes and Duodenal Contents After Secretin in the Diagnosis of Diseases of the Pancreas, Gastroenterology 32:212, 1957.

EDITORIALS

THE USES OF THE PAST

Sixty years ago Joseph Mathews of Louisville, Kentucky, called together the small group of American proctologists then available and, in Columbus, Ohio, organized the American Proctologic Society. Mathews, the first orthodox physician in the world to embark on proctology as a specialty, was then the immediate Past President of the American Medical Association—the culmination of a brilliant medical career—and was gratified that he could lend some measure of his prestige to the official organization of a new and small specialty.

At the annual meeting of the Society this June in Atlantic City and London, which celebrated the three score years of the existence of the organization and, in effect, the specialty, reviews of its achievements and prospects were the highlights. It was shown that continual changes, some noteworthy, some minor, have developed during the long years. Many of the surgical conditions of this field receive the same general type of treatment as they did 60 years ago, subject to those refinements of technic which have characterized other phases of surgery. On the other hand, new information, new skills and new adjuncts to surgical safety have revolutionized the surgeon's comprehension and the surgical treatment of many major lesions of the large bowel, among them ulcerative colitis, diverticular disease and cancer. Periodic reassessments of past progress and mistakes are valuable to any phase of medical endeavor for, as was pointed out in a previous editorial in this Journal, "knowing the history of medicine is like knowing the origin of words. It is very difficult to use them correctly until one understands the derivation and original meaning. Similarly, one applies current medical methods with much more facility if he is acquainted with the labored steps and stages of their development, the early inspirations and the early mistakes."

"The Uses of the Past" was the title given to a series of essays written by Herbert Muller in 1952. These were an inquiry into the way history works, concluding that mankind cannot count on miracles but must accept destruction or salvation, relying on our humanistic tradition for wisdom or, if necessary, consolation. The past does have its uses and it is never wholly lost. It remains with us and without this persistence of the past, life would lose all continuity.

Someone has said that today is always good because it links yesterday and tomorrow. From today we survey the panorama of the past with its gradual journey into now and because this vista brings with it the challenge of the future, we in medicine are wisely deterred from a smug complacency born of the victories of the present. While we cannot predict tomorrow, the past suggests that it may shame today.

No one will deprecate the gains which have accrued to humanity from advances in the field of medicine arising as they have from the use of exact, organized and classified knowledge. But, as Amos Koontz emphasized in a scholarly article in the July, 1956, issue of the *Maryland State Medical Journal,* cycles of past history reveal that, just as decadence follows in the wake of increasing demands for security, civilizations, as they reach their peak, invariably replace broad cultural trends by emphasis upon expediency or upon conformity to the unyielding frame of scholasticism. In medicine there is much to be said for the cultural phases of our profession which set it apart three score years ago from other vocations less dedicated to personal service. Our fathers practiced the art of medicine, striving for understanding wisdom as well as scientific progress.

As physicians, we must hope that old ideas will not be sacrificed for practical gains; as teachers, we must encourage not only intellectual proficiency but the more intangible spiritual values which provide a firm and indispensible anchor for the individual in society and which distinguish the great physician.

CURTICE ROSSER, M.D.

DERMATOMYOSITIS AND MALIGNANCY

From the middle 1880's until the turn of the century, the clinical syndrome of dermatomyositis evolved from various clinical reports and pathologic studies in the German literature of acute diseases of the muscles. Steiner[1] reported the first case in the American literature in 1905. Many different names were used in the earlier years in attempts to describe the varied complications or clinical manifestations accompanying certain of the cases. In general, dermatomyositis has been classified with others of the "collagen diseases." Over the past several decades the disease has been recognized more and more commonly. It has been accepted as the more common of the collagen diseases in childhood.

The relationship of dermatomyositis to the other so-called collagen diseases, just as the interrelationship of all of this group one to another, has been a controversial one. From pathologic considerations and from certain special laboratory investigations there are good reasons for thinking of dermatomyositis as distinct from disseminated lupus and periarteritis nodosa for example. (There has been a kinder acceptance for the thought of relationship of dermatomyositis to scleroderma.) On the other hand, from a clinical viewpoint one cannot but be impressed by certain similarities of dermatomyositis to the others of the collagen diseases, especially in its onset on occasion and some aspects of the clinical manifestations and course. More than once dermatomyositis has been thought of as rheumatic fever at its inception, later to develop into its truly recognizable state. Rheumatologists have time and again had the experience of considering a patient as an example of rheumatoid arthritis and then to have dermatomyositis show itself after months or even years of a "rheumatoid" course. Numerous authors have pointed to the manifestations characteristic of systemic lupus occurring in dermatomyositis, yet outlining the differentiation of these two entities. The apparent intimate relationship of dermatomyositis to disseminated lupus has been reported.[2,3] There are not infrequent references in the literature outlining the similarities and possible interrelationships of dermatomyositis and scleroderma.

There is another interesting aspect of dermatomyositis which has attracted increasing attention in recent years. This is its association with malignancy. The first case report of such association was by Stertz[4] in 1916, though the emphasis of this interrelationship is accredited to Bezecny[5] in his publication of 1935. The reported incidence of malignant neoplasms in cases of dermatomyositis have ranged from 5 to 18 per cent. Authors have called attention to the development of the clinical picture of dermatomyositis both before the neoplasm was discovered as well as its development during the course of known neoplasia. Also, it has been recognized that the clinical manifestations may disappear for the time being following the control of the malignant tumor by operation, irradiation, or hormonal therapy.

A review of the world's literature of this aspect of dermatomyositis has appeared recently. Williams[6] found 92 instances of malignancy reported in 590 cases of dermatomyositis with an almost equal incidence as between the sexes, the majority of the patients falling between the ages of 40 and 70 years. The distribution of cases among malignancies were as follows: stomach 16; breast 15; lung 14; ovary 10; lymphoma and leukemia 9; gallbladder 4; colon and rectum 4; kidney 3; uterus 3; and larynx three. A scattering appeared in lesser number among other malignant neoplasms. Among those who had a known tumor before the appearance of dermatomyositis, the interval from discovery of the tumor ranged from 3 weeks to 7 years. An amelioration of symptoms after treatment of the tumor appeared more often in instances of carcinoma of the ovary or breast.

The acute onset of dermatomyositis in the cases possibly related to malignancy may be dramatic, appearing mainly as a rash especially of the exposed areas, face, dorsum of hands, arms, neck and thorax. Often these have been known to occur after exposure to the sun. The subsequent course of muscular

1. Steiner, W. R.: Dermatomyositis With Report of a Case Which Presented a Rare Muscle Anomaly but Once Described in Man, J. Exper. Med. 6:407, 1905.
2. Kampmeier, R. H., and Smith, Luther E.: Diffuse Arteritis as a Recurrent Disease, Tr. Am. Clin. & Climatol. A. 65:232, 1953.
3. Talbot, John H., and Moleres-Ferrandix, R.: Collagen Diseases. New York, Grune & Stratton, 1956, p. 118.
4. Stertz, G.: Polymyositis, Berl. klin. Wchnschr. 1:489, 1916.
5. Bezecny, R.: Dermatomyositis, Arch. Dermat. u. Syph. 171:242, 1935.
6. Williams, R. C.: Dermatomyositis and Malignancy: A Review of the Literature, Ann. Int. Med. 50:1174, 1959.

involvement with its attendant clinical and laboratory findings then supervenes.

In his discussion Williams, in pointing to a 15.3% incidence of malignancy in dermatomyositis, correctly points to the possibility of this significantly high figure being artificial because of probable selection of cases for reporting. Yet the association seems to be more than one of chance. The author speculates as to the possible interrelationships of dermatomyositis and malignant tumor as, (1) the skin and muscle taking part in a "natural defense reaction to blood-borne carcinoma cells or cell products," and (2) an "endocrine imbalance" pointing particularly to the reported high incidence of cancers of breast and ovary in dermatomyositis.

One might well speculate on one aspect of the host relationship to a malignant tumor not touched upon by Williams. If one accepts a phenomenon of sensitivity of tissues to an antigen as the basis of pathogenesis in the collagen diseases (and there are good reasons for this hypothesis) one might hypothesize an endogenous "foreign" or abnormal protein derived from the malignancy as one cause of dermatomyositis. A temporary cessation or minimal production of such an antigen might be expected by the removal or treatment of a malignant process, and thereby account for an amelioration of the clinical manifestations of dermatomyositis.

In any event, the sudden appearance of a rash on the exposed surfaces in a middle-aged person should be of interest to the family doctor who may be consulted first for this unusually persisting "sunburn." The clinical implications if not common are at least interesting.

25 YEARS AGO

Periarteritis Nodosa (Necrotizing Arteritis) Associated with Rheumatic Heart Disease*

"In the last two years, of eight cases of typical periarteritis nodosa verified at necropsy, four presented conclusive evidence of rheumatic heart disease. This evidence consisted in all four cases of a history of rheumatic fever (i.e., acute polyarteritis accompanied by fever) and clinical findings of rheumatic cardiovalvular disease. Postmortem examination revealed characteristic gross and histologic features of rheumatic fever including in every case the presence of Aschoff bodies.

"In addition to the eight cases just mentioned the records of the department of pathology of the Mount Sinai Hospital show that the diagnosis of periarteritis nodosa was made in five other cases, in which the characteristic lesions were discovered at postmortem examination. Two of these five cases ran a febrile course with arthritis and presented clinical evidence of rheumatic valvular disease. Postmortem examination revealed, in addition to periarteritis nodosa, a verrucous endocarditis of the mitral valve in both cases and a large thrombotic mass involving an aortic commissure in one of them. No Aschoff bodies were found in the myocardium. Both cases ran the febrile course of a general infection accompanied by clinical evidence of glomerulonephritis. In neither case was a positive blood culture obtained. . . .

"Before discussing the significance of the not infrequent association of acute rheumatic fever with periarteritis nodosa as demonstrated in our cases, brief mention should be made of the criteria employed for the diagnosis of these conditions. For the purposes of this report we have assumed that the presence in the myocardium of typical Aschoff bodies was essential for the diagnosis of rheumatic heart disease. At the same time we must emphasize that in each of the cases reported there was, in addition, a history of febrile polyarteritis; in three this occurred during the final hospitalization. . . . Finally, at postmortem examination there were not only Aschoff bodies but other evidences of rheumatic carditis, such as acute auricular lesions, inflammation and vascularization of the valves, collagen necrosis, fibrinous pericarditis and characteristic rheumatic verrucous vegetations on the valves. . . .

"It is not our purpose in this report to enter into a discussion of the etiology or nature of rheumatic fever and periarteritis nodosa. Until we know more about them, we cannot say the final word as to their relationship to each other. The high incidence of rheumatic heart disease in this small series of cases of periarteritis nodosa is significant, and also the simultaneity of their clinical manifestations. In three of the four cases the symptoms of the final illness were due both to an acute attack of rheumatism and to the lesions of periarteritis nodosa. In the fourth case there were no obvious evidences of active rheumatic infection. Nevertheless, an acute rheumatic lesion was found in the heart. One must conclude that in these cases we were not dealing with two unrelated diseases, but that the periarteritis nodosa was one of the manifestations of the rheumatic infection. . . .

"Because of the frequency of the association of these diseases in our cases and the simultaneous occurrence of the symptoms of each, we believe it probable that rheumatic fever is a common cause of the vascular lesions termed periarteritis nodosa."

*Friedberg, Charles K., and Gross, Louis: Periarteritis Nodosa (Necrotizing Arteritis) Associated with Rheumatic Heart Disease, Arch. Int. Med. 54:170, 1934.

SOUTHERN MEDICAL NEWS

ALABAMA

Dr. Ward Pigman, Professor of Biochemistry at the University of Alabama Medical Center, will receive the 1959 Hudson Award of the American Chemical Society.

Dr. Richard Westbrook is the new President of the Birmingham District Dental Society succeeding Dr. Polly Ayers. Dr. Walter Kyle is President-Elect; Dr. Stanley Reynolds, Vice-President; Dr. Thomas W. Jones, Secretary; and Dr. Edwin M. Speed, Treasurer.

Dr. Robert Earl Roth, Birmingham, has been named Chairman of the Department of Radiology at the University of Alabama Medical Center.

Dr. James N. Sussex, formerly Associate Professor of Psychiatry at the University of Alabama Medical Center, Birmingham, has been named Professor and Chairman of the Department of Psychiatry.

Dr. Mervyn B. Quigley, Teacher-Trainee in Anatomy at the Medical and Dental Colleges of the University of Alabama, has been awarded a Senior Research Fellowship by the United States Public Health Service, through the Division of General Medical Sciences, National Institutes of Health.

Dr. Clark Gravlee, Birmingham, was recently awarded First Prize for his exhibit in the "Resident Division" by the American College of Obstetrics and Gynecology. The award came to Dr. Gravlee for his "Gravlee Gun," developed for the purpose of tying a newborn baby's umbilical cord.

Dr. H. Earle Conwell, Birmingham, has been made Chairman of the Committee of the Musculoskeletal Division of *Standard Nomenclature of Diseases and Operations,* published by the American Medical Association.

DISTRICT OF COLUMBIA

Dr. William B. Tucker, Director of Tuberculosis Service for the Veterans Administration in Washington, has been chosen the new President-Elect of the American Trudeau Society.

Dr. Ludwig G. Lederer, Medical Director for Capital Airlines, has been installed as President of the Aerospace Medical Association. Dr. William J. Kennard was chosen Secretary-Treasurer and Capt. Oran W. Chenault, Chief of Aviation Medicine in the Navy's Bureau of Medicine and Surgery, was elected First Vice-President.

The Board of Trustees of the Medical Service of the District of Columbia has elected Dr. James A. Dusbabek President of the Service, succeeding Dr. Donald Stubbs. Other officers elected are Dr. Henry L. Darner, First Vice-President; and Dr. A. C. Gray, Assistant Secretary.

The St. Elizabeths Hospital Medical Society has elected Dr. Leon Salzman, President; Dr. Francis N. Waldrop, Vice-President; and Dr. Luther Robinson, Secretary-Treasurer.

Dr. Roy T. Lester is the new Manager of the Washington Office of the American Medical Association. He succeeds Dr. Edwin Patterson.

New officers of the D. C. Trudeau Society are: Dr. J. Winthrop Peabody, Jr., President-Elect; Dr. Roy G. Klepser, Vice-President; and Dr. James P. Mann, Secretary-Treasurer.

Dr. Otis L. Anderson, who retired in July as Assistant Surgeon General for Personnel and Training, United States Public Health Service, has been named one of the AMA's medical liaison representatives in the Washington office.

Dr. William P. Herbst has been honored by the Georgetown Clinical Society with a Certificate of Merit, which is presented each year to a distinguished member of the Society.

Dr. George E. Schreiner has been elected President of the American Society for Artificial Internal Organs.

Dr. S. Ross Taggart has been appointed as Assistant Health Officer of Prince Georges County. Dr. Taggart, Chief of the Preventable and Chronic Disease Division, District Health Department, has been on the staff of the District Health Department for 30 years.

Dr. Aris Carpousis, at the meeting of the Civil Aviation Medical Association in Los Angeles, was elected to the post of National Vice-President.

Drs. Frank S. Pellegrini and Otis R. Farley have been elected Vice-Presidents of the Board of Trustees of the Greater Southeast Community Hospital Foundation. Nearly half of the one million dollar goal has been reached, contributions now totaling $420,000.

The following medical societies have elected as officers:

Washington Society for Pathologists. President, Dr. Thelma Dunn; Vice-President, Dr. William Newman; and Secretary-Treasurer, Dr. Daniel Weiss.

The Washington Psychiatric Society. Dr. Marvin L. Adland, President-Elect; Dr. Leon Yochelson, Secretary; and Dr. Morris Kleinerman, Treasurer.

The Montgomery County Pediatric Society. Dr. Carolyn H. S. Pincock, Silver Spring, President; Dr. Allen E. Marans, Silver Spring, Vice-President and President-Elect; Dr. Ralph Stiller, Silver Spring, Secretary; and Dr. Ira W. Pearlman, Chevy Chase, Treasurer.

Dr. John M. Keshishian, Instructor in Surgery at Georgetown University School of Medicine, is one of a medical team of 5 doctors and 2 nurses which is being sent to South Viet Nam through the joint efforts of the International Cooperation Administration and MEDICO. The medical group, all volunteers, will serve without pay. They will treat actual cases of pulmonary tuberculosis and demonstrate up-to-date methods of treatment of lung disease to Viet-Namese medical personnel in Saigon's Cho Ray Hospital.

FLORIDA

Dr. Maurice Edelman, Miami, has been elected a Fellow of the American Society of Facial Plastic Surgery.

Dr. Charles F. Tate, Jr., Miami, has been elected President of the Florida Trudeau Society succeeding Dr. Kip G. Kelso, Vero Beach. Other officers include: Dr. George H. McCain, Tallahassee, Vice-President; and Dr. Allen Y. DeLaney, Gainesville, Secretary.

Dr. Walter W. Sackett, Jr., Miami, has been appointed Vice-President of the General Practice Section of the North American Division of the Pan American Medical Association.

Dr. M. Jay Flipse, Miami, was elected President-Elect of the American College of Chest Physicians at their annual meeting, which was held June 3-7 at the Ambassador Hotel, Atlantic City, New Jersey.

Dr. J. G. Smith, Jr., Assistant Professor of Dermatology at the University of Miami School of Medicine, has been given the annual award of the American Dermatologic Association. The award was received at the association's annual meeting and was given "for his studies on 'The Aged Human Sebaceous Gland.'"

Dr. Ralph W. Jack, Miami, has been installed as President of the Florida Medical Association.

Dr. Lester R. Gragstedt, Chairman of the Department of Surgery at the School of Medicine, University of Chicago, Chicago, Illinois, will become Research Professor of Surgery at the School of Medicine, University of Florida.

GEORGIA

Drs. William D. Jennings, Jr., and Enon C. Hopkins, Augusta VA Hospital staff, have been certified as Diplomates in their respective medical specialties, Dr. Jennings by the American Board of Surgeons and Dr. Hopkins by the American Board of Internal Medicine.

Dr. Preston D. Ellington has been installed as President of the Augusta Area Tuberculosis Association.

Dr. Rudolph Bell, Thomasville, is the new President of the Southeastern Section of the American Urological Association.

Continued on page 64

BOOKS RECEIVED

A Doctor Remembers. By Edward H. Richardson, M.D., Associate Professor Emeritus of Gynecology, The Johns Hopkins University School of Medicine. 252 pages. New York: Vantage Press, Inc., 1959. Price $3.95.

Total Surgical Management. By James D. Hardy, M.D., Professor and Chairman, Department of Surgery, University of Mississippi Medical Center. 277 pages. New York: Grune & Stratton, 1959. Price $9.50.

Maternity. A Guide to Prospective Motherhood. By Frederick W. Goodrich, Jr., M.D. 127 pages. Englewood Cliffs, N. J., 1959. Price $1.75.

The Clinical Examination of Patients with Organic Cerebral Disease. By R. Klein, M.D. (Prague); and W. Mayer-Gross, M.D. (Heidelberg), F.R.C.P. (London). 96 pages. Springfield, Ill.: Charles C. Thomas, Publisher, 1959. Price $3.50.

Medical Education. Annotated Bibliography 1946-1955. World Health Organization. 390 pages. Columbia University Press, New York: 1958. Price $6.75.

The Physiopathology of Cancer. By 32 authors. Edited by Freddy Homburger, M.D. 1,167 pages. Second edition. New York: Paul B. Hoeber, Inc., 1959. Price $33.00.

Hey Groves' Synopsis of Surgery. Edited by Sir Cecil Wakeley, Bt., K.B.E., C.B., LL.D., Past President of the Royal College of Surgeons of England. Fifteenth edition. 601 pages. Baltimore: The Williams and Wilkins Company, 1958. Price $8.50.

The Effect of Pharmacologic Agents on the Nervous System. Proceedings of the Association. Research Publications, Volume 37. Edited by Francis J. Braceland, M.D. 470 pages, 124 illustrations. Baltimore: The Williams and Wilkins Company, 1959. Price $13.50.

The Pathology and Management of Portal Hypertension. By R. Milnes Walker, M.S., F.R.C.S., Professor of Surgery, University of Bristol. 110 pages. Baltimore: The Williams & Wilkins Company, 1958. Price $8.00.

Group Processes. Transactions of Fourth Conference, October, 1957. Edited by Bertram Schaffner, M.D., Columbia University. 252 pages. New York: Josiah Macy, Jr., Foundation, 1959. Price $4.50.

Aids to Medical Treatment. By T. H. Crozier, B.Sc., M.D., D.P.H., F.R.C.P., Physician to the Royal Victoria and Belfast City Hospitals. Fourth Edition, 361 pages. Baltimore: The Williams and Wilkins Company, 1959. Price $3.75.

Now or Never. By Smiley Blanton, M.D., with Arthur Gordon. 273 pages. Englewood Cliffs, N. J.: Prentice-Hall, Inc., 1959. Price $4.95.

Hypnosis in Modern Medicine. Edited by Jerome M. Schneck, M.D., Clinical Associate Professor of Psychiatry, State University of New York College of Medicine. Second edition, 356 pages. Springfield, Ill.: Charles C. Thomas, Publisher, 1959. Price $8.75.

INSTRUCTIONS TO CONTRIBUTORS

Exclusive Publication: Articles offered for publication must be contributed solely to the Southern Medical Journal.

Manuscripts: Manuscripts should be original copy, typewritten, double-spaced, with wide margins. Because of lack of space, it is necessary to limit the number of bibliographic references to twenty. Footnotes and references should conform to the following style:

1. Doe, J. E.: What You Should Know about It, New England J. Med. 243:435, 1950.

Illustrations: Black and white glossy prints, preferably 5 by 7 inches, and drawings in India ink on white paper are required. The author's name, number and indication of top, if doubtful, should be attached. Necessary plates not exceeding six, or one and a half pages, will be furnished by the Journal.

Reprints: Reprints are available at publisher's cost. An order form will accompany author's galley proof and should be returned with the galley to the Editor.

Book Reviews: Books and monographs submitted for review should be mailed to the Editor. Acknowledgment will appear in the Journal. Selection rights reserved.

Editorial Address: All manuscripts, corrected galley proof, reprint orders, books for review and related correspondence should be addressed to the Editor, R. H. Kampmeier, M.D., Vanderbilt University School of Medicine, Nashville 5, Tennessee.

Business Address: All correspondence related to membership, subscriptions, advertising, and other business should be addressed to the Southern Medical Association, 2601 Highland Avenue, Birmingham 5, Alabama.

BOOK REVIEWS

Diseases of Children in the Subtropics and Tropics

By H. C. Trowell, M.D., Senior Specialist Physician, Paediatric Unit, Mulago Hospital and Makerer College, University College of East Africa, Kampala, Ugando; and D. B. Jelliffe, M.D., Visiting Professor of Tropical Medicine, Tulane University School of Medicine, New Orleans, La. 901 pages. London: Edward Arnold, Publisher, Ltd., 1958. Price $18.50.

This is a comprehensive book covering the common diseases affecting children in tropical and subtropical areas all over the world. The various conditions are discussed by authorities with first-hand clinical experience and include many conditions which are found in the temperate zones. It is not just another book on parasitosis. A discussion of the importance of socio-economic factors and their influence on health and disease in the various areas concerned adds to the completeness and interest of the book.

This is a complete reference under one cover and should prove to be extremely valuable to any physician dealing primarily with children.

Temporal Lobe Epilepsy

Edited by Maitland Baldwin, M.D., Associate Professor of Clinical Neurosurgery, Georgetown University School of Medicine, Washington, D. C.; and Pearce Bailey, Ph.D., M.D., Professor, Clinical Neurology, Georgetown University School of Medicine, Washington, D. C. 561 pages. Springfield, Ill.: Charles C. Thomas, Publisher, 1958. Price $15.50.

This volume contains the reports and discussion of the Second International Colloquium on Temporal Lobe Epilepsy. Thirty-eight well-known investigators have contributed to this colloquium, and the editors have wisely included all of the discussions reflecting the various opinions expressed during the meeting. The reports in this volume indicate the multidisciplinary nature of the approaches to this problem. The neuroanatomic, neurophysiologic, neurochemical and neuropathologic considerations are well delineated by the contributors. The electroencephalographic aspects and the results of surgical treatment are other subjects which will be of interest to neurologists and neurosurgeons. The editors and sponsors of this work are to be congratulated upon assembling the reports of so many eminent investigators into this one volume. It is highly recommended to all clinicians, neuroanatomists, neuropathologists, and psychologists who have an interest in this field.

Radiation Protection

By Carl B. Braestrup, Associate, Department of Radiology, Columbia University, N. Y.; and Harold O. Wyckoff, Chief, Radiation, Physics Laboratory, National Bureau of Standards, Washington, D. C. 348 pages. Springfield, Ill.: Charles C. Thomas, Publisher, 1958. Price $10.50.

This very valuable book brings together, probably for the first time, a considerable amount of data which has previously required a search of the literature from a variety of sources. It deals with the production and various types of radiation, also the measurement and biologic effects, various methods of shielding and the criteria for protection necessary in diagnostic and therapeutic radiology, as well as in industrial and other nonmedical fields. Radioactive isotope laboratory design for convenience and proper protection, as well as disposal, is well covered. Medical use of radioisotopes, as well as agricultural and industrial use are discussed.

The book covers radiation protection from practically all aspects and all types of radiations in present day use. It is useful to students, research workers, residents, radiologists, as well as the other fields in which radioactive materials and x-ray machines are now used.

It is a very well conceived and readable book.

History of Medicine in Louisiana. Vol. 1

Edited by John Duffy. 509 pages. Baton Rouge, La.: Louisiana State University Press, 1958. Price $10.00.

To southern physicians and particularly those living along the Gulf Coast this volume will be of exceeding interest and most enjoyable reading. Anyone who ever knew Dr. Rudolph Matas will readily realize with what enthusiasm he must have embarked on gathering the data on medical practice during the French and Spanish regimes beginning with the settlement of the Gulf Coast, the founding of New Orleans and the subsequent development of this settlement into the city it now is. Those early doctors assigned to the care of the military and of the civilian populations were a most interesting breed, and hardy ones at that. They were in general medical officers of either the Army or Navy assigned by the King of France to the duties just mentioned. Of particular interest is the importance attached to the midwives who were commissioned to apply their profession in the early settlements, being in some instances carefully selected as capable women and assigned by the French government to the early settlements of the Gulf Coast.

The book contains many stories which illustrate the medicolegal aspects of medicine in those days as related to the civilian population and especially to the care of slaves and the responsibility of this care by the owner. Court proceedings are of interest. The descriptions of epidemics, the founding of hospitals and their equipment and the like make the time pass quickly in reading this historical volume.

Dr. Matas worked well in the collecting of the data, and the author has used this to good effect in producing a most readable and enjoyable book for pastime reading. As one who has lived on the Gulf Coast and in New Orleans and been interested in the medical life of the area, the reviewer says without equivocation that this has been one of the most interesting, historical books he has read.

The Art of Listening

By Dominick A. Barbara, M.D., Practicing Psychoanalyst Associated with the American Institute for Psychoanalysis. 192 pages. Springfield, Ill.: Charles C. Thomas, Publisher, 1958. Price $5.50.

The author, a psychoanalyst associated with the American Institute for Psychoanalysis and Member of the Medical Board of the Karen Horney Clinic, is no newcomer to the field of speech and hearing. His "Stuttering—A Psychodynamic Approach to Its Understanding and Treatment" appeared in 1954 followed by "Your Speech Reveals Your Personality" in 1958.

Here he surveys the art of listening from many angles. Beginning with a description of end organ function, Dr. Barbara notes the extent of the problem of defective hearing and then takes off into his own special field, discussing the sensory deficit in infant and child development, the dynamics of speech and language in personality structure, the psychogenic defenses against hearing and finally certain means whereby listening skills may be improved. The chapter entitled, as was Theodore Reik's book, "Listening with the Third Ear," points out values and errors in therapeutic interviewing. "The Sound of Silence" has words of wisdom for our chatting, noisy society.

Dr. Barbara's book is well documented and indexed. His sources cover a wide range—from Freud to Clifton Fadiman. This is an exceedingly readable book with value for all who seek to understand and help others. If the scope is too broad to prevent some superficiality the bibliography may lead the reader to further exploration.

The Story Behind the Word

By Harry Wain, M.D. 342 pages. Springfield, Ill.: Charles C. Thomas, Publisher, 1958. Price $8.50.

This book serves as an incomplete dictionary. It seems to be most useful when dealing in eponyms since a very brief historical note accompanies the name. Minimal attempts are made at defining a term though certainly the gist of each word is made clear. It is impossible to read as one might expect of any dictionary. In rare instances the origin of the use of a word would have been more interesting, at least to this reviewer, than its derivation.

In his introduction the author indicates that over five thousand medical terms have been included. A great deal of effort has been expended with little expectation that it will evoke much interest. It would be valuable in the library of a medical historian or one interested in that aspect of medicine.

The Excitable Cortex in Conscious Man

By Wilder Penfield, O.M., C.M.G., Litt.B., M.D., D.Sc., F.R.C.S., (Hon.) F.R.C.P., F.R.S., Director of the Montreal Neurological Institute, McGill University, Montreal. 42 pages. Springfield, Ill.: Charles C. Thomas, Publisher, 1958. Price $2.50.

This publication of the Fifth Sherrington Lecture includes a very literate introduction in which Dr. Penfield reminisces about his association with Sir Charles Sherrington. After presenting his hypothesis regarding the centrencephalic system, the results of electrical stimulation of various portions of the cerebral cortex are described. There follows a series of illustrative case reports regarding the results of stimulation of the exposed cortex of the temporal lobe. Direct quotations of the conscious patient reacting to these stimuli illustrate the author's thesis. The conclusions are briefly and clearly stated and an excellent bibliography is appended.

This little volume will be of interest to all medical students and physicians, and particularly to those with a special interest in the nervous system.

The Clinical Examination of the Nervous System

By G. H. Monrad-Krohn, M.D., Professor Emeritus of Medicine (Neurology) in the University of Oslo. 453 pages. New York and London: Paul B. Hoeber, Inc., 1958. Price $9.50.

This reviewer has exhausted all superlatives in describing previous editions of this monumental work on the examination of the nervous system. The author, in what is probably the last preface to this work which he will write, emphasizes the need for stressing the clinical aspects of neurologic disorders. The sections on synkinetic movements, aphasia, and intracranial circulation have been expanded. This book remains primarily the work of a gifted clinician and the additions which have been made with the assistance of Professor Sigvald Refsum, the author's successor at the University of Oslo, enhance the usefulness of this volume. It is highly recommended to all students and practitioners.

Physiology of Spinal Anesthesia

By Nicholas M. Greene, B.S., M.A., M.D., Professor of Anesthesiology and Pharmacology, Yale University School of Medicine. 195 pages. Baltimore: The Williams and Wilkins Co., 1958. Price $6.00.

Dr. Greene's excellent book contains chapters on The Central Nervous System, The Cardiovascular System, The Respiratory System; Hepatic, Renal, Endocrine, and Gastrointestinal Function; Metabolism and Acid-Base Balance, and Obstetrical Physiology. Each chapter consists of an extensive, detailed discussion of the pertinent physiology and anatomy, of the system under discussion, followed by an analysis of the effects of spinal anesthesia on the system. Methods and technics of minimizing or avoiding harmful consequences of spinal anesthesia are extensively discussed. Throughout the book information is concisely and clearly presented; many references to original articles are included on all points covered. Safer and more efficient use of spinal anesthesia should result from careful study of this text.

Textbook of Neurology

By H. Houston Merritt, M.D., Professor of Neurology, Columbia University; Director of the Service of Neurology, Neurological Institute, Presbyterian Hospital. Second edition. 710 pages. Philadelphia: Lea and Febiger, 1959. Price $12.00.

In this second edition of a relatively new textbook of Neurology, it is significant that Wilson's hepatolenticular degeneration is now listed under diseases due to inborn metabolic defects. This work reflects the dy-

namic spirit of modern neurology in its approach to the diagnosis and treatment of diseases of the nervous system.

Some minor errors which were present in the first edition have been corrected although the basic plan of the first edition has been retained. Again, the author is to be congratulated upon the manner in which he has related neurology to the general field of internal medicine. This textbook is highly recommended to all students and practitioners.

Recent Advances in Paediatrics

Edited by Douglas Gairdner, Associate Lecturer in Paediatrics, University of Cambridge. 372 pages. Boston: Little, Brown and Company, 1958. Price $9.50.

This is an excellent and timely review of the following subjects: Changes in the Circulation at Birth and The Effects of Asphyxia, The Hematology of Infancy, Jaundice in the Newborn, Physical Growth, Hypothyroidism, Spina Bifida Cystica, Hydrocephalus of Infancy, The Nephrotic Syndrome, Tuberculosis, Rheumatic Fever, The Deaf Child, and Pyogenic Osteitis.

Although some of the subjects are not commonly encountered, they are nonetheless important and are becoming more so because of the advances made in the last few years. The first chapter seems unnecessarily long and involved with animal experiments but will serve to point out the many problems of the newborn in becoming adjusted at birth.

This book will make an excellent reference book for any physician on the subjects discussed.

Tuberculosis and Other Communicable Diseases

By J. Arthur Myers, M.D., Professor of Internal Medicine and Public Health, University of Minnesota. 427 pages. Springfield, Ill.: Charles C. Thomas, Publisher, 1959. Price $14.50.

This text covers the most important communicable diseases affecting man. As the title would imply, the section on tuberculosis is the lengthiest, but nothing really new is added. The chapter on acute respiratory diseases is excellent. These diseases are well classified by the author; information is up to date and well documented. In like manner, the chapter on the common cold is the best this reviewer has yet encountered. Most of the other chapters are well-written, proper emphasis being placed on the epidemiology of each disease discussed. Slightly disconcerting is the paucity of illustrations. All in all, however, this text should find good use in the hands of the medical and nursing student and practitioner.

Officers of the Southern Medical Association 1958-1959

President

Dr. Milford O. Rouse, 1414 Medical Arts Building, Dallas 1, Texas

President-Elect

Dr. Edwin Hugh Lawson, 2700 Napoleon Avenue, New Orleans 15, Louisiana

First Vice-President

Dr. Tom D. Spies, Nutrition Clinic, Hillman Hospital, Birmingham 5, Alabama

Second Vice-President

Dr. Edwin L. Zander, 3330 Canal Street, New Orleans 19, Louisiana

Executive Secretary-Treasurer and Managing Editor

Mr. V. O. Foster, 2601 Highland Avenue, Birmingham 5, Alabama

Advisor and Professional Relations Counselor

Mr. C. P. Loranz, 2601 Highland Avenue, Birmingham 5, Alabama

Business Manager

Mr. Robert F. Butts, 2601 Highland Avenue, Birmingham 5, Alabama

Editor of Journal

Dr. R. H. Kampmeier, Vanderbilt University School of Medicine, Nashville 5, Tennessee

Councilors

Dr. Harry Lee Claud, *Chairman,* Suite 1010, 1835 Eye Street, N.W., Washington 6, D. C.

Dr. Robert D. Moreton, *Vice-Chairman,* 1217 W. Cannon Street, Fort Worth 4, Texas

Dr. J. Garber Galbraith, 2020 15th Avenue, South, Birmingham 5, Alabama

Dr. Fount Richardson, 316 West Dickson Street, Fayetteville, Arkansas

Dr. Joseph S. Stewart, 3384 Mary Street, Miami 33, Florida

Dr. Jack C. Norris, 138 Doctors Building, 490 Peachtree Street, N.E., Atlanta, Georgia

Dr. J. Duffy Hancock, 705 Brown Building, Louisville 2, Kentucky

Dr. M. M. Hattaway, Magnolia Medical Center, 4440 Magnolia Street, New Orleans 15, Louisiana

Dr. Harry M. Robinson, Jr., 1209 St. Paul Street, Baltimore 2, Maryland

Dr. Guy T. Vise, 2120 Fourth Street, Meridian, Mississippi

Dr. O. P. J. Falk, #3 Southmoor, Clayton 5, Missouri

Dr. George D. Wilson, 308 City Hall Building, Asheville, North Carolina

Dr. Vernon D. Cushing, Pasteur Medical Building, 711 North West Tenth, Oklahoma City 3, Oklahoma

Dr. J. W. Jervey, Jr., 709 Dunbar Street, Greenville, South Carolina

Dr. A. H. Lancaster, 608 W. Main Street, Knoxville 2, Tennessee

Dr. Donald S. Daniel, Johnston-Willis Hospital, Richmond 21, Virginia

Dr. Howard A. Swart, 524 Medical Arts Building, Charleston 1, West Virginia

Executive Committee of the Council

Dr. Harry Lee Claud, Chairman of the Council, *Chairman*

Dr. Robert D. Moreton, Vice-Chairman of the Council

Dr. J. W. Jervey, Jr.

Dr. George D. Wilson

Dr. Jack C. Norris

Dr. Milford O. Rouse, *President*

Dr. Edwin Hugh Lawson, *President-Elect*

Board of Trustees

(All are Past Presidents)

Dr. Walter C. Jones, *Chairman*, (1959), 550 Brickell Avenue, Miami 32, Florida

Dr. Alphonse McMahon, (1960), Missouri Theatre Building, St. Louis 3, Missouri

Dr. R. L. Sanders, (1961), 20 South Dudley Street, Suite 306 B, Memphis 3, Tennessee

Dr. W. Raymond McKenzie, (1962), Medical Arts Building, Baltimore 1, Maryland

Dr. J. P. Culpepper, Jr., (1963), 709 Arledge Street, Hattiesburg, Mississippi

Dr. W. Kelly West, (1964), 520 Osler Building, Oklahoma City 3, Oklahoma

Editorial Board

Dr. Lenox D. Baker, Duke University School of Medicine, Durham, North Carolina

Dr. Sullivan G. Bedell, 1103 Barrs Street, Jacksonville 4, Florida

Dr. Willis E. Brown, University of Arkansas School of Medicine, Little Rock, Arkansas

Dr. Stanley A. Hill, 607 Fillmore Street, Corinth, Mississippi

Dr. John H. Lamb, Medical Arts Building, Oklahoma City 2, Oklahoma

Dr. Preston A. McLendon, 2146 Wyoming Avenue, N.W., Washington 8, D. C.

Dr. J. F. A. McManus, University of Alabama Medical Center, Birmingham 5, Alabama

Dr. William F. Rienhoff, Jr., 1201 North Calvert Street, Baltimore, Maryland

Dr. Charles Rieser, 819 Cypress Street, N.E., Atlanta 8, Georgia

Dr. Curtice Rosser, 710 Medical Arts Building, Dallas 1, Texas

Section Officers

Section on Allergy

Dr. George J. Stuart, *Chairman*, 1150 Connecticut Avenue, N.W., Washington 6, D. C.

Dr. William C. Grater, *Vice-Chairman*, 1719 Pacific Avenue, Dallas 1, Texas

*Dr. Thomas E. Van Metre, *Secretary*, 1014 St. Paul Street, Baltimore 2, Maryland

*Dr. John P. McGovern, *Secretary-Elect*, 3509 Montrose Boulevard, Houston 6, Texas

Section on Anesthesiology

Dr. John T. Stage, *Chairman*, Riverside Hospital, 2033 Riverside Avenue, Jacksonville 4, Florida

Dr. John B. Parmley, *Vice-Chairman*, Hotel Dieu, New Orleans, Louisiana

*Dr. Lester Rumble, Jr., *Secretary*, Suite #3, 82 Baker Street, Atlanta 3, Georgia

Section on Dermatology and Syphilology

*Dr. Joseph M. Hitch, *Chairman*, 127 W. Hargett Street, Raleigh, North Carolina

*Dr. Joseph L. Rankin, *Vice-Chairman*, 384 Peachtree Street, N.E., Atlanta 8, Georgia

Dr. J. Fred Mullins, *Secretary*, 927 Strand Street, Galveston, Texas

Section on Gastroenterology

Dr. Tim J. Manson, *Chairman*, 103 Interstate Building, Chattanooga 2, Tennessee

*Dr. J. Spalding Schroder, *Vice-Chairman*, P. O. Box 459, Emory University Clinic, Atlanta 22, Georgia

Dr. George E. Welch, *Secretary*, Browne-McHardy Clinic, 3636 St. Charles Avenue, New Orleans 15, Louisiana

Section on General Practice

Dr. H. B. Goodwin, Jr., *Chairman*, 117 N. Fifth Street, P. O. Box 657, Fort Pierce, Florida

*Dr. Malcolm H. Harris, *Vice-Chairman*, West Point, Virginia

Dr. Carroll L. Witten, *Secretary*, 2237 Taylorsville Road, Louisville 5, Kentucky

Section on Gynecology

Dr. John T. Armstrong, *Chairman*, 426 Hermann Professional Building, 6410 Fannin Street, Houston 25, Texas

Dr. Robert N. Creadick, *Vice-Chairman*, Box 3608, Duke University Medical Center, Durham, North Carolina

*Dr. Wm. Durwood Suggs, *Secretary*, 1213 West Franklin Street, Richmond 20, Virginia

Section on Industrial Medicine and Surgery

Dr. W. G. Thuss, Sr., *Chairman*, Thuss Clinic, 2230 North 3rd Avenue, Birmingham 3, Alabama

Dr. L. A. Pyle, Jr., *Vice-Chairman,* The Chesapeake & Potomac Telephone Companies, 722 12th Street, N.W., Washington 5, D. C.

*Dr. A. N. Sam Houston, *Secretary,* 912 Union Street, New Orleans 12, Louisiana

Section on Medicine

Dr. Ellard M. Yow, *Chairman,* Baylor University College of Medicine, Texas Medical Center, Houston 25, Texas

Dr. Kelly M. West, *Chairman-Elect,* Department of Medicine, University of Oklahoma School of Medicine, 801 N.E. 13th Street, Oklahoma City 4, Oklahoma

*Dr. Thomas J. Anderson, Jr., *Vice-Chairman,* 501 Doctors Building, 478 Peachtree Street, N.E., Atlanta 8, Georgia

Dr. Kelly T. McKee, *Secretary,* Medical College Hospital, 55 Doughty Street, Charleston, South Carolina

Section on Neurology and Psychiatry

Dr. Theodore L. L. Soniat, *Chairman,* Ochsner Clinic, 3503 Prytania Street, New Orleans 15, Louisiana

Dr. Robert H. Groh, *Chairman-Elect,* 1726 M Street, N.W., Washington 6, D. C.

*Dr. Joe E. Tyler, *Secretary,* Springer Clinic, 604 So. Cincinnati, Tulsa 19, Oklahoma

Section on Obstetrics

Dr. Charles H. Mauzy, Jr., *Chairman,* Bowman Gray School of Medicine, Winston-Salem, North Carolina

Dr. Simon V. Ward, *Vice-Chairman,* 4414 Magnolia Street, New Orleans 15, Louisiana

*Dr. John D. Gordinier, *Secretary,* 806 Heyburn Building, Louisville 2, Kentucky

Section on Ophthalmology and Otolaryngology

Dr. G. S. Fitz-Hugh, *Chairman,* 104 East Market Street, Charlottesville, Virginia

Dr. George M. Haik, *Chairman-Elect,* 812 Maison Blanche Building, New Orleans 16, Louisiana

*Dr. B. Russell Burke, *Vice-Chairman,* Suite 147, 490 Peachtree Street, N.E., Atlanta 8, Georgia

Dr. Mercer G. Lynch, *Secretary,* Ochsner Clinic, Prytania and Aline Streets, New Orleans 15, Louisiana

Section on Orthopedic and Traumatic Surgery

Dr. A. H. Weiland, *Chairman,* 263 Aragon Avenue, Coral Gables, Florida

Dr. Daniel C. Riordan, *Vice-Chairman,* 1538 Louisiana Avenue, New Orleans 15, Louisiana

*Dr. H. Robert Brashear, Jr., *Secretary,* North Carolina Memorial Hospital, Chapel Hill, North Carolina

Section on Pathology

Dr. Oscar B. Hunter, Jr., *Chairman,* 915 19th Street, N.W., Washington 6, D. C.

*Dr. John T. Godwin, *Vice-Chairman,* 265 Ivy Street, N.E., Atlanta 3, Georgia

Dr. Warren B. Matthews, *Secretary,* c/o Kennestone Hospital, Marietta, Georgia

Section on Pediatrics

Dr. McLemore Birdsong, *Chairman,* University of Virginia Hospital, Charlottesville, Virginia

*Dr. Victor C. Vaughan III, *Vice-Chairman,* Medical College of Georgia, Augusta, Georgia

*Dr. Theodore C. Panos, *Secretary,* University of Arkansas Medical Center, Little Rock, Arkansas

Section on Physical Medicine and Rehabilitation

Dr. Herbert W. Park, *Chairman,* Medical College of Virginia, Box 846, Richmond 19, Virginia

Dr. Torsten H. Lundstrom, *Chairman-Elect,* VAC Hospital, Mountain Home, Tennessee

*Dr. Solomon Winokur, *Secretary,* 4729 Prytania Street, New Orleans 15, Louisiana

Section on Proctology

Dr. F. J. Burns, *Chairman,* 4660 Maryland Avenue, St. Louis 8, Missouri

*Dr. Fred B. Hodges, Jr., *Vice-Chairman,* 403 Medical Arts Building, 384 Peachtree Street, N.E., Atlanta 8, Georgia

Dr. Patrick H. Hanley, *Secretary,* 3503 Prytania Street, New Orleans 15, Louisiana

Section on Public Health

Dr. William W. Schottstaedt, *Chairman,* 800 N.E. 13th Street, Oklahoma City 4, Oklahoma

*Dr. Robert L. Simmons, *Vice-Chairman,* 1542 Tulane Avenue, New Orleans 12, Louisiana

*Dr. T. Oscar Vinson, *Secretary,* Director, De Kalb County Health Department, 126 Trinity Place, Decatur, Georgia

Section on Radiology

Dr. Ted F. Leigh, *Chairman,* Emory University Clinic, Atlanta 22, Georgia

Dr. J. Maxey Dell, Jr., *Vice-Chairman,* 217 S. Main Street, Gainesville, Florida

*Dr. Seymour Ochsner, *Secretary,* Ochsner Clinic, 3503 Prytania Street, New Orleans 15, Louisiana

Section on Surgery

*Dr. Joseph M. Donald, *Chairman,* 1316 South 19th Street, Birmingham 5, Alabama

*Dr. Guy W. Horsley, *Vice-Chairman,* 617 W. Grace Street, Richmond 20, Virginia

*Dr. M. L. Michel, *Secretary,* 1441 Delachaise Street, New Orleans 15, Louisiana

Section on Urology

Dr. H. King Wade, Jr., *Chairman,* 231 Central Avenue, Hot Springs, Arkansas

*Dr. Max Mayo Green, *Vice-Chairman,* 4440 Magnolia Street, New Orleans 15, Louisiana

*Dr. William H. Morse, *Secretary,* 188 So. Bellevue Street, Memphis 4, Tennessee

---

*New Officers—Elected New Orleans Meeting, 1958.

New wide-use dosage form

of the outstanding

anticholinergic-antispasmodic

PRO-BANTHĪNE®

TABLETS

(HALF STRENGTH)

Pro-Banthīne (Half Strength) has been especially designed for your prescribing convenience.

This new form provides flexibility of dosage from low levels of one tablet t.i.d. for patients with minimal distress, to one or two tablets every 2 or 3 hours for those with more pronounced symptoms.

Primary indications are gastrointestinal spasm, bladder spasm, maintenance therapy of peptic ulcer and "irritable bowel" syndrome. The lower dosage also has a field of usefulness in smooth muscle spasm of children and geriatric patients.

when your prescription reads—

℞ *Pro-Banthīne Tablets (Half Strength)*

—the pharmacist will dispense this new size (7½ mg.)

PRO-BANTHĪNE *(brand of propantheline bromide)*

Dosage forms:
Pro-Banthīne tablets (15 mg.)
Pro-Banthīne tablets (Half Strength) (7½ mg.)
Pro-Banthīne ampuls (30 mg.)

G. D. Searle & Co., Chicago 80, Ill. *Research in the Service of Medicine.*

Good tasting to patients

Good riddance to worms

VERMIZINE eliminates pinworms and roundworms without alienating the patient. Its delicious strawberry flavor spells "umm!" for the patient, and its piperazine gluconate content spells sudden death for unwanted parasites.

VERMIZINE is virtually nontoxic, well tolerated, highly effective and economical. There are no contraindications at normal dosage. Try it in your next "wormy" case.

Formula: Each cc. contains piperazine gluconate, equivalent to piperazine hexahydrate 100 mg.

Supply: Bottles containing pints and gallons.

Vermizine

CHICAGO PHARMACAL COMPANY

CHICAGO, ILL. • SAN FRANCISCO, CALIF.

Digitalis

in its completeness

Each pill is
equivalent to
one USP Digitalis Unit

Physiologically Standardized
therefore always
dependable.

Clinical samples sent to physicians upon request.

Davies, Rose & Co., Ltd.
Boston, 18, Mass.

Don't forget, Doctor—
"to take some of your own medicine!"

On vacation – at the beach – on the golf course – or gardening in your own back yard, sunburn, insect bites, cuts and abrasions are all part of the summer picture.

A handy tube of Xylocaine Ointment means prompt relief of pain, itching and burning for your patients. After you've seen to your patients' comfort, remember that tube of Xylocaine Ointment for yourself.

Just write "Xylocaine Ointment" on your Rx blank or letterhead, and we will send a supply for you and your family.

Astra Pharmaceutical Products, Inc., Worcester 6, Mass., U.S.A.

XYLOCAINE® OINTMENT
(brand of lidocaine*)

2.5% & 5%

SURFACE ANESTHETIC

SEE PDR

*U.S. Pat. No. 2,441,498 Made in U.S.A.

If she needs nutritional support . . . she deserves

GEVRAL®

Vitamin-Mineral Supplement Lederle

CAPSULES—14 VITAMINS—11 MINERALS

LEDERLE LABORATORIES, a Division of AMERICAN CYANAMID COMPANY
Pearl River, New York

?

What is the diagnosis...

Mrs. X, age 35—physical findings negative.

Complaints: Constipation, alternating with periods of diarrhea, tenesmus, flatulence, colicky pains, easy fatigability, anorexia, periodic dull headaches and muscle pains.

Many times these symptoms point to *E. histolytica*, the parasite most often misdiagnosed,[1] and far more prevalent than generally suspected.[2,3,4]

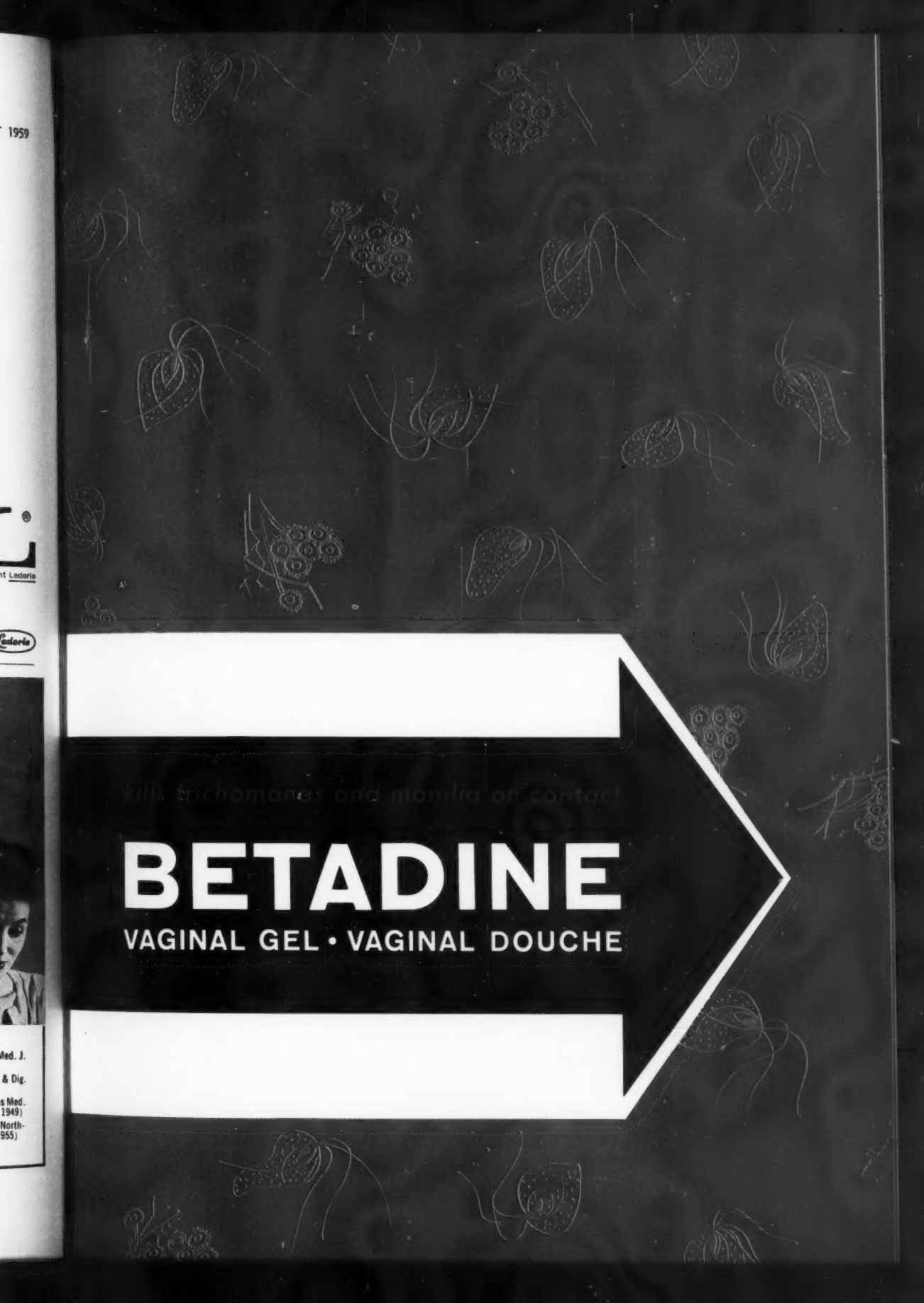
Accurate diagnosis of amebiasis can be made with the MOAN TEST on a single 5 cc. blood sample. More dependable than fecal examination; no special laboratory equipment or training.

Write for descriptive literature:

MOBAC LABORATORIES

85 Lansdowne Avenue • Lansdowne, Penna.

1. Elsdon-Dew, R.: S. Afr. Med. J. 32:89 (Jan., 1958)
2. Webster, B. H.: Am. Pract. & Dig. Treat. 9:897 (June, 1958)
3. D'Antoni, J. S.: New Orleans Med. & Surg. J. 102:55 (Aug., 1949)
4. Rinehart, R. E., Marcus, H.: Northwest Med. 54:708 (July, 1955)


kills trichomonas and monilia on contact
BETADINE
VAGINAL GEL • VAGINAL DOUCHE

BETADINE

brand of Povidone-Iodine, possesses broad-range germicidal activity against fungi, yeasts, bacteria, protozoa, and viruses. In the vaginal tract Betadine Vaginal Gel and Betadine Vaginal Douche kill trichomonas and monilia on contact and destroy common pathogens. Betadine is virtually nonirritating to vaginal mucosa.

indicated:

in the treatment of trichomoniasis, moniliasis and nonspecific vaginitis.

advantages:

- almost immediate relief from leukorrhea, pruritus; diminishes malodor
- unsurpassed broad-range microbicidal activity
- therapeutically active even in the presence of blood, pus, vaginal secretions
- wetting action to assist penetration into vaginal crypts and crevices

how to use:

In the office: Swab the vaginal vault with Betadine Antiseptic, full strength.

prescribe Betadine Vaginal Douche for therapeutic use as follows: Two (2) tablespoonfuls to a quart of lukewarm water once daily by the patient at home, for six days. On the seventh day, the patient returns for re-examination and swabbing with Betadine Antiseptic; an additional week of therapeutic douching if necessary.

prescribe Betadine Vaginal Gel as follows: Insert one (1) applicatorful of Betadine Vaginal Gel each night, followed by a douche the next morning, through the entire menstrual cycle. If further therapy is warranted, the gel should be continued only during the actual menses days of the following two menstrual periods.

After the infection has been brought under control, the use of Betadine Vaginal Douche is recommended twice weekly at a dilution of one (1) tablespoonful to a quart of lukewarm water.

established in 1905

TAILBY-NASON COMPANY, INC., Dover, Delaware

BETADINE® VAGINAL GEL

1 OZ. TUBE WITH APPLICATOR

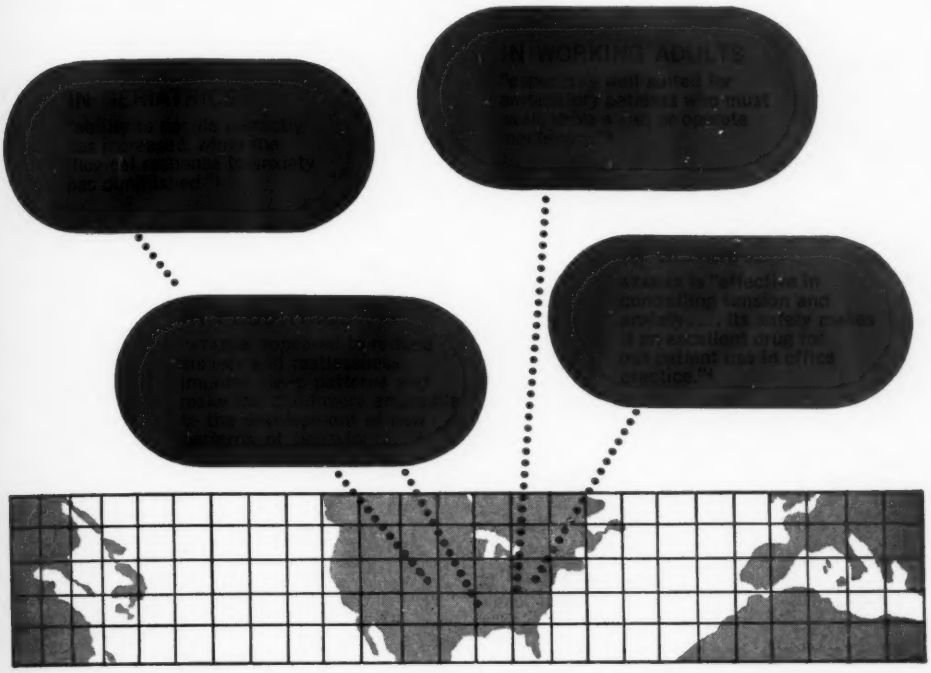
BETADINE® VAGINAL DOUCHE

8 OZ. BOTTLE

re-evaluating tranquilizers?

READ WHAT CLINICIANS ARE NOW SAYING ABOUT ATARAX®

(brand of hydroxyzine)



INVESTIGATORS AGREE ON OPTIMAL ATARAX DOSAGES

For childhood behavior disorders	10 mg. tablets	3-6 years, one tablet t.i.d. over 6 years, two tablets t.i.d.
	Syrup	3-6 years, one tsp. t.i.d. over 6 years, two tsp. t.i.d.
For adult tension and anxiety	25 mg. tablets	one tablet q.i.d.
	Syrup	one tbsp. q.i.d.
For severe emotional disturbances	100 mg. tablets	one tablet t.i.d.
For adult psychiatric and emotional emergencies	Parenteral Solution	25-50 mg. (1-2 cc.) intramuscularly, 3-4 times daily, at 4-hour intervals. Dosage for children under 12 not established.

Supplied: Tablets, bottles of 100. Syrup, pint bottles. Parenteral Solution, 10 cc. multiple-dose vials.

References: 1. Smigel, J. O., et al.: J. Am. Ger. Soc., in press. 2. Freedman, A. M.: Pediat. Clin. North America 5:573 (Aug.) 1958. 3. Ayd, F. J., Jr.: New York J. Med. 57:1742 (May 15) 1957. 4. Menger, H. C.: New York J. Med. 58:1684 (May 15) 1958. 5. Coirault, M., et al.: Presse méd. 64:2239 (Dec. 26) 1956. 6. Bayart, J.: Presented at the International Congress of Pediatrics, Copenhagen, Denmark, July 22-27, 1956.

ATARAX®

Roerig

New York 17, N. Y.
Division, Chas. Pfizer & Co., Inc.
Science for the World's Well-Being

NIAMID*

the mood brightener

Lifts the burden of depression... opens the way for a sunnier outlook

New areas of therapy

NIAMID is clinically effective in a broad range of depressive states, including: involutional melancholia, senile depression, postpartum depression, reactive depression, the depressive stage of manic-depressive disease, and schizophrenic depressive reaction.

A wide variety of psychoneurotic depressions as in general practice also respond effectively to NIAMID. Depression associated with the menopause and with postoperative states, and depression accompanying chronic or incurable diseases such as gastrointestinal and cardiovascular disorders, arthritis, and inoperable cancer, can now be treated successfully with NIAMID.

NIAMID is also strikingly effective for many complaints, mild or severe, vague or well defined, when due to masked depression rather than to organic disease. This masked depression may take the form of guilt feelings, crying spells or sadness, difficulty in concentration, loss of energy or drive, insomnia, emotional fatigue, feelings of hopelessness or helplessness, loss of interest in normal activity, listlessness, apprehension or agitation, and loss of appetite and weight.

While tranquilizers have had some measure of effectiveness in many of these areas, NIAMID now gives the practicing physician a new, safe drug for the specific treatment of depression without the risk of increasing the depressive symptoms.

New safety

The outstanding safety of NIAMID in extensive clinical trials eliminates the hepatotoxic reactions observed with the first of the monoamine oxidase inhibitors. These reactions have not been seen with NIAMID.

Acute and chronic toxicity studies show this distinctive freedom from toxicity. Moreover, during the extensive clinical trials of NIAMID by a large number of investigators, not only has no liver damage been reported, but only in a very few isolated instances have hypotensive effects been seen.

The absence of toxicity may be the result of the unique carboxamide group in the NIAMID molecule. This structure may explain why NIAMID is excreted largely unchanged in the urine, with only insignificant quantities of potentially free hydrazine being formed. Previously, where a monoamine oxidase inhibitor had been associated with hepatic toxicity there was some evidence that substantial quantities of free hydrazine were formed in the body.

Background of NIAMID

A major advance in the treatment of mental depression came with a newer understanding of the influence of brain serotonin and norepinephrine on the mood. Levels of both these neuro-hormones are decreased in animals under experimental conditions analogous to depression; relief of these model depressions is seen with a rise in the levels of both serotonin and norepinephrine.

A second advance came with the development of monoamine oxidase inhibitors, substances which raise the cerebral level of both serotonin and norepinephrine. The first of the amine oxidase inhibitors raised the cerebral level of serotonin, but did not appear to raise that of norepinephrine level proportionately.

Pfizer *Science for the world's well-being*™

PFIZER LABORATORIES

Division, Chas. Pfizer & Co., Inc., Brooklyn 6, N. Y.

Attention at Pfizer Research was then directed to a new drug that would overcome this disadvantage. NIAMID significantly raises the cerebral level of *both* serotonin and norepinephrine under experimental conditions.

The dramatic discovery of NIAMID now makes available an extremely effective, safe antidepressant for the successful treatment of a full range of depressive states.

Precautions

Side effects are most often minor and mild manifestations of central nervous system stimulation, modifiable by reduction in dosage; these may take the form of restlessness, insomnia, headache, weakness, vertigo, dry mouth, and perspiration. Care should be taken when NIAMID is used with chlorothiazide compounds, since hypotensive effects have been noted in some patients receiving combined therapy—even though hypotension has rarely been noted with NIAMID alone. There has been no evidence of liver damage in patients on NIAMID; however, in patients who have any history of liver disease, the possibility of hepatic reactions should be kept in mind.

Dosage and Administration

Start with 75 mg. daily in single or divided doses. After a week or more, revise the daily dosage upward or downward, depending upon the response and tolerance, in steps of one or one-half 25 mg. tablet. Once satisfactory response has been attained, the dosage of NIAMID may be reduced gradually to the maintenance level.

The therapeutic action of NIAMID is gradual, not immediate. Many patients respond within a few days, others satisfactorily in 7 to 14 days. Some patients, particularly chronically depressed or regressed psychotics, may need substantially higher dosages (as much as 200 mg. daily has been used) and prolonged administration before responses are achieved.

Supply

NIAMID is available in: 25 mg., pink, scored tablets in bottles of 100; and 100 mg., orange, scored tablets in bottles of 100.

References

Complete bibliography and Professional Information Booklet are available on request.

*TRADEMARK FOR BRAND OF NIALAMIDE

NIAMID
the mood brightener

NIAMID*

the mood brightener

Lifts the burden of depression... opens the way for a sunnier outlook

New areas of therapy

NIAMID is clinically effective in a broad range of depressive states, including: involutional melancholia, senile depression, postpartum depression, reactive depression, the depressive stage of manic-depressive disease, and schizophrenic depressive reaction.

A wide variety of psychoneurotic depressions seen in general practice also respond effectively to NIAMID. Depression associated with the menopause and with postoperative states, and depression accompanying chronic or incurable diseases such as gastrointestinal and cardiovascular disorders, arthritis, and inoperable cancer, can now be treated successfully with NIAMID.

NIAMID is also strikingly effective for many complaints, mild or severe, vague or well defined, which are due to masked depression rather than to organic disease. This masked depression may take the form of guilt feelings, crying spells or sadness, difficulty in concentration, loss of energy or drive, insomnia, emotional fatigue, feelings of hopelessness or helplessness, loss of interest in normal activity, listlessness, apprehension or agitation, and loss of appetite and weight.

While tranquilizers have had some measure of effectiveness in many of these areas, NIAMID now gives the practicing physician a new, safe drug for the specific treatment of depression without the risk of increasing the depressive symptoms.

New safety

The outstanding safety of NIAMID in extensive clinical trials eliminates the hepatotoxic reactions observed with the first of the monoamine oxidase inhibitors. These reactions have not been seen with NIAMID.

Acute and chronic toxicity studies show this distinctive freedom from toxicity. Moreover, during the extensive clinical trials of NIAMID by a large number of investigators, not only has no liver damage been reported, but only in a very few isolated instances have hypotensive effects been seen.

The absence of toxicity may be the result of the unique carboxamide group in the NIAMID molecule. This structure may explain why NIAMID is excreted largely unchanged in the urine, with only insignificant quantities of potentially free hydrazine being formed. Previously, where a monoamine oxidase inhibitor had been associated with hepatic toxicity, there was some evidence that substantial quantities of free hydrazine were formed in the body.

Background of NIAMID

A major advance in the treatment of mental depression came with a newer understanding of the influence of brain serotonin and norepinephrine on the mood. Levels of both these neuro-hormones are decreased in animals under experimental conditions analogous to depression; relief of these model depressions is seen with a rise in the levels of both serotonin and norepinephrine.

A second advance came with the development of monoamine oxidase inhibitors, substances which raise the cerebral level of both serotonin and norepinephrine. The first of the amine oxidase inhibitors raised the cerebral level of serotonin, but did not appear to raise that of norepinephrine level proportionately.

Pfizer *Science for the world's well-being*™

PFIZER LABORATORIES

Division, Chas. Pfizer & Co., Inc., Brooklyn 6, N. Y.

Attention at Pfizer Research was then directed to a new drug that would overcome this disadvantage. NIAMID significantly raises the cerebral level of *both* serotonin and norepinephrine under experimental conditions.

The dramatic discovery of NIAMID now makes available an extremely effective, safe antidepressant for the successful treatment of a full range of depressive states.

Precautions

Side effects are most often minor and mild manifestations of central nervous system stimulation, modifiable by reduction in dosage; these may take the form of restlessness, insomnia, headache, weakness, vertigo, dry mouth, and perspiration. Care should be taken when NIAMID is used with chlorothiazide compounds, since hypotensive effects have been noted in some patients receiving combined therapy—even though hypotension has rarely been noted with NIAMID alone. There has been no evidence of liver damage in patients on NIAMID; however, in patients who have any history of liver disease, the possibility of hepatic reactions should be kept in mind.

Dosage and Administration

Start with 75 mg. daily in single or divided doses. After a week or more, revise the daily dosage upward or downward, depending upon the response and tolerance, in steps of one or one-half 25 mg. tablet. Once satisfactory response has been attained, the dosage of NIAMID may be reduced gradually to the maintenance level.

The therapeutic action of NIAMID is gradual, not immediate. Many patients respond within a few days, others satisfactorily in 7 to 14 days. Some patients, particularly chronically depressed or regressed psychotics, may need substantially higher dosages (as much as 200 mg. daily has been used) and prolonged administration before responses are achieved.

Supply

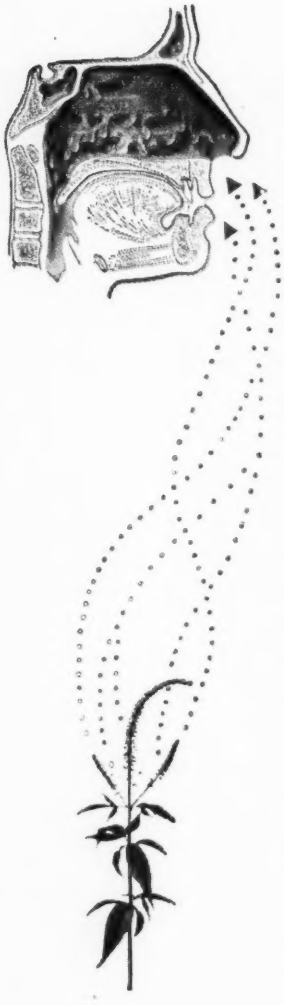
NIAMID is available in: 25 mg., pink, scored tablets in bottles of 100; and 100 mg., orange, scored tablets in bottles of 100.

References

Complete bibliography and Professional Information Booklet are available on request.

*TRADEMARK FOR BRAND OF NIALAMIDE

NIAMID
the mood brightener



when pollen allergens attack the nose...

Triaminic provides more effective therapy in respiratory allergies because it combines two antihistamines[1,2] with a decongestant.

These antihistamines block the effect of histamine on the nasal and paranasal capillaries, preventing dilation and exudation.[3] *This is not enough;* by the time the physician is called on to provide relief, histamine damage is usually present and should be counteracted.

The decongestive action of orally active phenylpropanolamine helps contract the engorged capillaries, reducing congestion and bringing prompt relief from nasal stuffiness, rhinorrhea, sneezing and sinusitis.[4,5]

TRIAMINIC is orally administered, systemically distributed and reaches *all* respiratory membranes, avoiding nose drop addiction and rebound congestion.[6,7] TRIAMINIC can be prescribed for prompt relief in summer allergies, including hay fever.

References: 1. Sheldon, J. M.: Postgrad. Med. **14**:465 (Dec.) 1953. 2. Hubbard, T. F. and Berger, A. J.: Annals Allergy p. 350 (May-June) 1950. 3. Kline, B. S.: J. Allergy **19**:19 (Jan.) 1948. 4. Goodman, L. S. and Gilman, A.: Pharmacol. Basis Ther., Macmillan, New York, 1956, p. 532. 5. Fabricant, N. D.: E.E.N.T. Monthly **37**:460 (July) 1958. 6. Lhotka, F. M.: Illinois M.J. **112**:259 (Dec.) 1957. 7. Farmer, D. F.: Clin. Med. **5**:1183 (Sept.) 1958.

Triaminic®

TRIAMINIC provides around-the-clock freedom from hay fever and other allergic respiratory symptoms with just one tablet q. 6-8 h. because of the special timed-release design.

Each TRIAMINIC timed-release tablet provides:

Phenylpropanolamine HCl	50 mg.
Pheniramine maleate	25 mg.
Pyrilamine maleate	25 mg.

Also available: TRIAMINIC SYRUP for those patients of all ages who prefer a liquid medication. Each 5 ml. teaspoonful is equivalent to ¼ Triaminic Tablet or ½ Triaminic Juvelet. TRIAMINIC JUVELETS provide half the dosage of the Triaminic Tablet with the same timed-release action for prompt and prolonged relief.

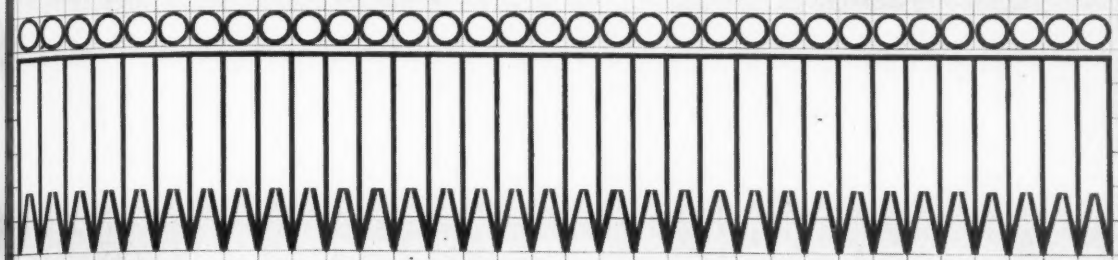
STOP *running noses* *and open stuffed noses orally*

SMITH-DORSEY • a division of The Wander Company • Lincoln, Nebraska • Peterborough, Canada

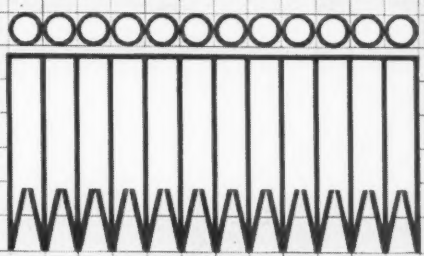
Decadron®

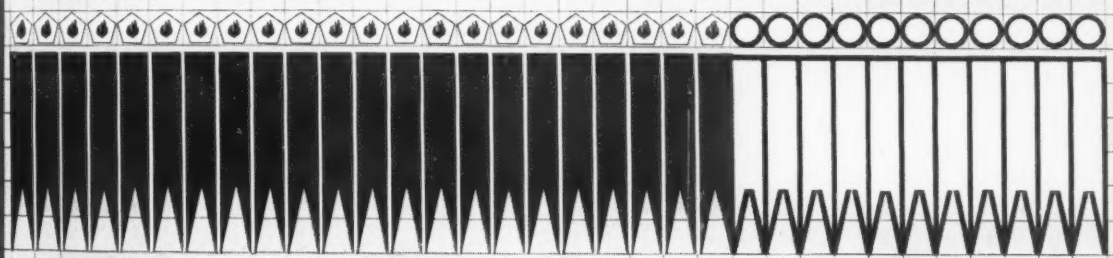
DEXAMETHASONE

treats more patients more effectively...



Of 45 arthritic patients
who were refractory
to other corticosteroids*





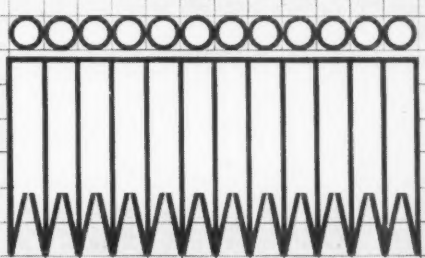
22 were successfully
treated with **Decadron**[1,2]

1. Boland, E. W., and Headley, N. E.: Paper read before the Am. Rheum. Assoc., San Francisco, Calif., June 21, 1958.
2. Bunim, J. J., et al.: Paper read before the Am. Rheum. Assoc., San Francisco, Calif., June 21, 1958.

*Cortisone, prednisone and prednisolone.

DECADRON is a trademark of Merck & Co., Inc.

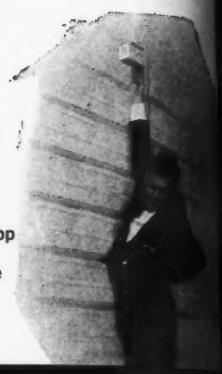
Additional information on DECADRON is available to physicians on request.



MSD Merck Sharp & Dohme

DIVISION OF MERCK & CO., INC., PHILADELPHIA 1, PA.

REACHING FOR THOSE 9B's NEARLY PUT ME ON THE SHELF...



Reaching for 9B shoes and other top shelf sizes is no joke . . . it gave me a terrible kink in my back.

Before the day was over, I could hardly stoop to push a shoehorn.

I called my doctor that night and picked up the tablets he prescribed.

The pain went away fast—in just 15 minutes—and I was back on the job the next morning! But not one 9B customer came in the whole day!

Percodan®-Demi & Percodan® *Tablets*

Salts of Dihydrohydroxycodeinone and Homatropine, plus APC

FOR PAIN

ACTS FASTER – usually within 5-15 minutes. **LASTS LONGER** – usually 6 hours or more. **MORE THOROUGH RELIEF** – permits uninterrupted sleep through the night. **RARELY CONSTIPATES** – excellent for chronic or bedridden patients. **VERSATILE** – new "demi" strength permits dosage flexibility to meet each patient's specific needs. PERCODAN-DEMI provides the PERCODAN formula with one-half the amount of salts of dihydrohydroxycodeinone and homatropine.

AVERAGE ADULT DOSE: 1 tablet every 6 hours. May be habit-forming. Federal law permits oral prescription.

Each PERCODAN® Tablet contains 4.50 mg. dihydrohydroxycodeinone hydrochloride, 0.38 mg. dihydrohydroxycodeinone terephthalate, 0.38 mg. homatropine terephthalate, 224 mg. acetylsalicylic acid, 160 mg. phenacetin, and 32 mg. caffeine.

AND THE PAIN WENT AWAY FAST

Endo®

Literature? Write
ENDO LABORATORIES
Richmond Hill 18, New York

*U.S. Pat. 2,628,185

designed

for

control of

diarrhea

AND
RELIEF OF INFLAMMATIONS
AND ACUTE UPSETS OF THE
GASTROINTESTINAL TRACT

RHEASTAT

Each fluidounce contains:

PHENOBARBITAL	¼ gr. (16.2 mg.)
HYOSCYAMINE SULFATE	0.1286 mg.
ATROPINE SULFATE	0.0250 mg.
HYOSCINE HYDROBROMIDE	0.0074 mg.

Sedative and Antipasmodic

KAOLIN, COLLOIDAL	90 gr. (6 Gm.)
PECTIN	5 gr. (0.32 Gm.)

Adsorbent and Detoxicant

SODIUM	6 mEq.
POTASSIUM	4 mEq.

Ion Replacement

IN A SPECIAL ALUMINUM HYDROXIDE GEL

Antacid

USUAL ADULT DOSE
1 OR 2 TABLESPOONFULS
EVERY 3 OR 4 HOURS

VANPELT & BROWN, INC., Richmond 4, Va.

unexcelled

potentiation · efficacy · toleration

in broad-spectrum antibiotic therapy

COSA-TERRAMYCIN®
oxytetracycline with glucosamine

capsules	*oral suspension*	*pediatric drops*
125 mg. 250 mg.	peach flavored, 125 mg. per teaspoonful (5 cc.), 2 oz. bottle	peach flavored, 100 mg. per cc. (5 mg. per drop), 10 cc. bottle (with calibrated dropper)

Science for the world's well-being
Pfizer
PFIZER LABORATORIES
Division, Chas. Pfizer & Co., Inc.
Brooklyn 6, N. Y.

150,000 PHYSICIANS
THE WORLD OVER DEPEND ON
THE INTEGRITY BEHIND THIS NAME

BIRTCHER

CARDIOGRAPH CARDIOSCOPE
DEFIBRILLATOR HEARTPACER
ELECTROSURGICAL UNITS
HOSPITAL-CLINIC-OFFICE
ULTRASONICS DIATHERMY
INFRARED ULTRAVIOLET
GALVANIC UNITS
ELECTROMUSCLE STIMULATORS
THE VIBRABATH
and
THE FAMOUS HYFRECATOR

Los Angeles 32, California

If he needs nutritional support . . .

he deserves

GEVRAL®

Vitamin-Mineral Supplement Lederle

CAPSULES—14 VITAMINS—11 MINERALS

LEDERLE LABORATORIES, a Division of
AMERICAN CYANAMID COMPANY, Pearl River, New York

Lederle

APPLICATION FOR HOTEL ACCOMMODATIONS

53rd ANNUAL MEETING

Atlanta, Georgia

November 16, 17, 18, and 19, 1959

Please Complete this Application and forward to Atlanta Address Now!

A Housing Bureau has been established for your convenience in making hotel reservations in Atlanta for the forthcoming meeting of the Southern Medical Association. Comparable room rates are listed. *Use the Reservation Blank below.* Please specify your first, second and third choice hotel. All requests for reservations should give: (1) anticipated date and hour of arrival; (2) date and approximate hour of departure; and (3) names and addresses of all persons who will occupy the accommodations. ALL RESERVATIONS SHOULD BE CLEARED THROUGH THE HOUSING BUREAU. Since all requests for rooms will be handled in chronological order, you should mail your application as early as possible. All reservations will be confirmed. The Municipal Auditorium will be General Headquarters.

Hotel	Single	Double Bed	Twin Beds	Suite
Atlanta Biltmore	$ 8.00–12.00	$10.00–16.00	$12.00–16.00	$25.00–75.00
Atlantan	5.00– 7.50	7.00– 9.50	9.00–12.00	18.00–20.00
Briarcliff	6.00–10.00	10.00–14.00	12.00–16.00	18.00–30.00
Clermont	4.00– 5.50	6.00– 7.50	7.00– 7.50	10.00–15.00
Cox Carlton	5.50– 6.50	8.00– 9.00	8.00– 9.00	16.00–18.00
Dinkler Plaza	7.00–12.50	10.00–12.50	14.00–16.50	36.50–56.50
Georgia	5.00 8.00	7.00–12.00	8.50–12.00	18.00–25.00
Georgian Terrace	6.00– 8.00	8.00–10.00	8.50–12.00	12.00–30.00
Henry Grady	7.00–14.00	10.00–16.00	11.00–16.00	20.00–35.00
Peachtree Manor	6.00– 8.00	8.50–12.00	8.50–12.00	14.00–32.00
Peachtree on Peachtree	6.00– 7.00	8.50–10.50	9.50–11.50	16.00–26.00
Piedmont	6.00– 9.00	9.50–11.00	10.00–15.00	25.00–30.00
Motels				
Atlanta Cabana	10.00–14.00	13.00–15.00	15.00–16.00	32.00
Heart of Atlanta	9.00	12.00	13.00–14.00	24.00–26.00
The Riviera	Rates Unannounced	(To open April, 1959)		
Downtown Motel	9.00–11.00		11.00–14.00	

HOUSING BUREAU
SOUTHERN MEDICAL ASSOCIATION
720 Rhodes-Haverty Building
Atlanta 3, Georgia

Please reserve the following accommodations for me for the Southern Medical Association Meeting:

Hotel Preference	Kind of Accommodations Desired
1st Choice.....	.....Single room at $.....to $.....
2nd Choice.....	.....Double room at $.....to $.....
3rd Choice.....	.....Twin bedroom at $.....to $.....
	.....Other type.....
Arrival Date.....	.....hour.....a.m.....p.m.
Departure Date.....	.....hour.....a.m.....p.m.

THE NAME OF EACH HOTEL GUEST MUST BE LISTED. Include the names of all persons for whom you are requesting reservations and who will occupy the room (s):

Name of Occupant (s) (Please type or print)	Address
.....	.....
.....	.....
.....	.....

Individual Requesting Reservations
(Please type or print)

Name.....

Address.....

City.....Zone.....

State.....

If the hotels of your choice are unable to accept your reservation, the Housing Bureau will make as good a reservation as possible elsewhere.

From:

_____

_____

_____

PLACE
STAMP
HERE

HOUSING BUREAU
Southern Medical Association
720 Rhodes-Haverty Building
Atlanta 3, Georgia

FIRST FOLD HERE

SECOND FOLD HERE

THIRD FOLD HERE

for your G.U. patients **FREEDOM**

from pain, infection and drug-induced complications

FURADANTIN®

brand of nitrofurantoin

FREEDOM FROM PAIN AND INFECTION

"Nitrofurantoin [FURADANTIN] was effective clinically, with a pronounced improvement, indicated by the appearance of the urine as well as by verbal commendation by the patient, within 24 to 36 hours.... Some of these patients with seemingly impossible cases were cured of their infection."[1]

"During the initial week of therapy, when the dose of nitrofurantoin was 100 mg. four times a day, the urine became free of pus and bacteria. Symptoms of urinary frequency, urgency, and dysuria were relieved."[2]

FREEDOM FROM DRUG-INDUCED COMPLICATIONS

- No significant development of bacterial resistance in over 7 years.
- No irreversible toxic effects on kidneys, liver, blood-forming organs or central nervous system ever reported.
- No monilial superinfection or staphylococcic enteritis ever reported.
- No fatalities from FURADANTIN therapy; the margin of safety is 90 to 1.
- "The drug was given continuously and safely for as long as three years."[2]

AVERAGE FURADANTIN ADULT DOSAGE: One 100 mg. tablet q.i.d. taken with meals and at bedtime with food or milk. Available as Tablets, 50 and 100 mg.; Oral Suspension, 25 mg. per 5 cc. tsp.

REFERENCES: 1. Stewart, B. L., and Rowe, H. J.: J. Am. M. Ass. **160**:1221, 1956. 2. Lippman, R. W., et al.: J. Urol., Balt. **80**:77, 1958.

NITROFURANS—a *unique* class of antimicrobials—neither antibiotics nor sulfonamides

EATON LABORATORIES, NORWICH, NEW YORK

A LESS "STORMY" COURSE FOR SOME POORLY CONTROLLED DIABETICS THANKS TO DIABINESE®

brand of chlorpropamide

The specific pharmacologic properties of DIABINESE—high activity, freedom from metabolic degradation, and gradual excretion—permit (1) prompt lowering of elevated blood sugar levels *without a "loading" dose*, and (2) smooth, sustained maintenance "devoid of...marked blood sugar fluctuations"[2] on convenient, lower-cost, once-a-day dosage. This is the consensus of extensive clinical literature.[1-11] Widespread use of DIABINESE since its introduction has confirmed the low incidence of side effects reported by the original investigators.

Thus, DIABINESE merits *first* consideration for any diabetic presently receiving or potentially better managed with oral therapy—including many diabetics for whom previous oral agents have proved ineffective.

Supplied: Tablets, white, scored 250 mg., bottles of 60 and 250; 100 mg., bottles of 100.

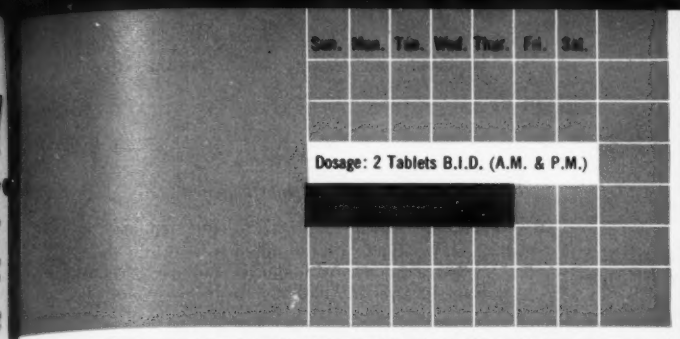
tablets / once-a-day dosage

"...has proved to be extremely useful in improving the control of the patient who has been uncontrolled on other regimens."[1]

Pfizer *Science for the world's well-being*

PFIZER LABORATORIES, Brooklyn 6, New York
Division, Chas. Pfizer & Co., Inc.

1. Dobson, H., et al.: Ann. New York Acad. Sc. 74:940, 1959. 2. Greenhouse, B.: Ibid., p. 643. 3. Forsham, P. H.; Magid, G. J., and Dorosin, D. E.: Ibid., p. 672. 4. Beaser, S. B.: Ibid., p. 701; New England J. Med. 259:573, 1958. 5. Bloch, J., and Lenhardt, A.: Ann. New York Acad. Sc. 74:954, 1959. 6. O'Driscoll, B. J.: Lancet 2:749, 1958. 7 Hadley, W. B.; Khachadurian, A., and Marble, A.: Ann. New York Acad. Sc. 74:621, 1959. 8. Duncan G. G.; Schless, G. L., and Deneshkieh, M. M. A.: Ibid., p. 717. 9. Handelsman, M. B.; Levitt. L., and Colabretta, M. F.: Ibid., p. 632. 10. Hills, A. G., and Abelove, W. A.: Ibid., p. 845. 11. Drey, N. W., et al.: Ibid., p. 962.



in premenstrual tension

only neo Bromth®

treats the whole syndrome

It was the introduction of neo Bromth several years ago that created such widespread interest in the premenstrual syndrome—because of neo Bromth's specific ability to prevent the development of the condition in the first place.

The action of neo Bromth is not limited merely to control of abnormal water retention, or of nervousness, or of pain—or any other single or several of the multiple manifestations characteristic of premenstrual tension. neo Bromth effectively controls the *whole* syndrome.

neo Bromth is also completely free from the undesirable side effects associated with such limited-action therapy as ammonium chloride, hormones, tranquilizers and potent diuretics. neo Bromth has continued to prove to be the safest—as well as the most effective—treatment for premenstrual tension.

Each 80 mg. tablet contains 50 mg. Pamabrom, and 30 mg. pyrilamine maleate. Dosage is 2 tablets twice daily (morning and night) beginning 5 to 7 days before menstruation. Discontinue when the flow starts.

BRAYTEN PHARMACEUTICAL COMPANY - Chattanooga 9, Tennessee

TUCKER HOSPITAL, INC.

212 West Franklin St.

RICHMOND, VIRGINIA

A private hospital for diagnosis and treatment of psychiatric and neurological patients. Hospital and out-patient services.

(Organic diseases of the nervous system, psychoneuroses, psychosomatic disorders, mood disturbances, social adjustment problems, involutional reactions and selective psychotic and alcoholic problems.)

DR. HOWARD R. MASTERS
DR. WEIR M. TUCKER
DR. AMELIA G. WOOD
DR. JAMES ASA SHIELD
DR. GEORGE S. FULTZ, JR.
DR. ROBERT K. WILLIAMS

Continued from page 997

The First District Medical Society announces new officers as follows: Dr. Randall G. Brown, Swainsboro, President; Dr. William H. Fulmer, Savannah, President-Elect; Dr. Albert M. Deal, Statesboro, Vice-President; Dr. David Robinson, Savannah, Secretary; and Dr. John Mooney, Statesboro, Treasurer.

Dr. Luther H. Wolff, Columbus, has been installed as President of the Medical Association of Georgia. Serving with him will be Drs. Milford B. Hatcher, Macon, President-Elect; Corbett H. Thigpen, Augusta, First Vice-President; W. P. Rhyne, Albany, Second Vice-President; and Chris J. McLoughlin, Atlanta, Secretary.

The annual "Georgia General Practitioner Award" was presented to Dr. J. C. Logan, Plains, who has practiced for more than fifty years.

KENTUCKY

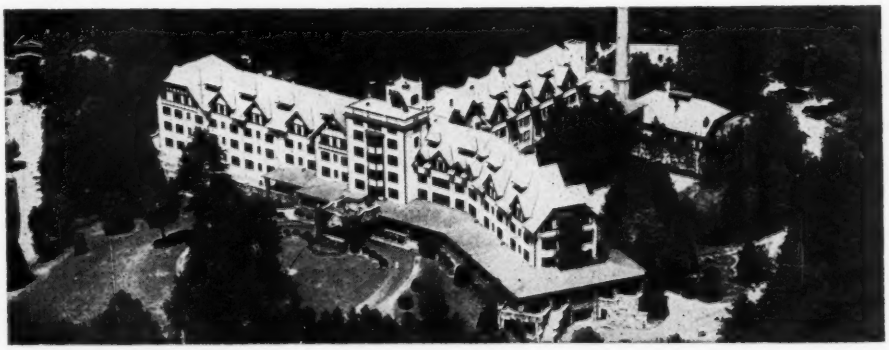
Dr. Carroll L. Witten, Louisville, has been chosen "Family Doctor of the Year" by the Kentucky Academy of General Practice. The award was given at the Academy's annual assembly in Louisville. Dr. Witten, Secretary of the Section on General Practice of the Southern Medical Association, is the youngest physician ever to receive this award.

Dr. Joseph B. Parker, Jr., Associate Professor of Psychiatry at the Duke University School of Medicine

Continued on page 66

Appalachian Hall • Asheville, North Carolina

ESTABLISHED 1916



An Institution for the diagnosis and treatment of Psychiatric and Neurological illnesses, rest, convalescence, drug and alcohol habituation.

Insulin Coma, Insulin Sub-Shock, Electroshock and Psychotherapy are employed. The Institution is equipped with complete laboratory facilities including electroencephalography and X-ray.

Appalachian Hall is located in Asheville, North Carolina, a resort town, which justly claims an all around clime for health and comfort. There are ample facilities for classification of patients, rooms single or en suite.

WM. RAY GRIFFIN, JR., M.D.
ROBERT A. GRIFFIN, M.D.
MARK A. GRIFFIN, M.D.
MARK A. GRIFFIN, JR., M.D.

For rates and further information write APPALACHIAN HALL, ASHEVILLE, N. C.

*1. Borrus, J. C.: J.A.M.A. 157:15[illegible] 11 30, [illegible] 2. Selli[illegible] S.: J.A.M.A. 157:1594, April 30, 1955. 3. Lenere, F.: [illegible]thwest Med. [illegible]98, Oct. [illegible]5. 4. Bene[illegible] B. and M[illegible]ocutti, C.: Lav. neuropsichiat. 18:693, 1[illegible]5. Selli[illegible].: J. Clin [illegible] Exper. Psy[illegible]th. 17:7[illegible]arch 1956. 6. Berglund, M., Blumenthal, B [illegible]lordh, P.: [illegible]ska läk. 5[illegible]3362. Dec. [illegible]1956. 7 [illegible]el, H. A., Wood, J. A. and Dixon, H. H.: [illegible]w York Acad[illegible]. 67:780, May 9, 1957. [illegible]Hollister[illegible]., Elkins, H., Hiler, E. G. and St. Pierr[illegible] Ann. New Yo[illegible] Acad. Sc. 67:789, May 9, [illegible]957. 9. G[illegible]: Rass. med. 34:233, July-Aug[illegible]57. 10[illegible]i, R. et al.: J. Pediat. P[illegible]axis 20:27, [illegible]g. 1957. [illegible]Niklund, P[illegible]: Anaesthesist [illegible]7, Aug[illegible]. 12. Tucker, W. I.: Sout[illegible]. J. 50:1111, Sept. 195[illegible]3. Rolandi[illegible]: Attual. ostet. [illegible]3(6[illegible]9, Nov.-Dec. 1957. 14. [illegible]ecker, W.: Klin. Mon[illegible]1. Augenh[illegible]2):224, 1958. [illegible]ebiance[illegible]G. and Cerqui, T.: Oto-r[illegible]ing. ital. 26(2):143, 1958. 16. [illegible]o, G.: Minerv[illegible]9:1914, 1958. 17. [illegible]uso, R. and [illegible]ti, F.: Ac[illegible]eurol. [illegible]3(1):36, J[illegible]1958. 18. [illegible]Gazz. med. ital. [illegible]9, Feb. [illegible]astur, R.[illegible]: J. Indian M. Prof[illegible]13 Feb. 1958. [illegible]t, W.: Therap. [illegible]97:66, Fe[illegible]l. B[illegible].: Lyon méd. 19[illegible] March 2, 1958. [illegible]iglia, G.: Mine[illegible]10:218, M[illegible]15, 1958. [illegible]lander, H. S.: [illegible] Cardiol. 1:395, [illegible]1958. 24. McCle[illegible]: Arch. Pe[illegible]75:101, [illegible]25. Sprauer, V. J.: Internat. Rec. Med. [illegible] GP Clinics 171:[illegible]1958. 26. [illegible]inson, R.[illegible] Robinson, H. M., Jr.: South. M. J. 51:[illegible]9, April 1958. 27. [illegible]S. and Fe[illegible]er, L.: N[illegible]ed. 58:1285, April 15, 1958. 28. Bouquerel, J., Naviau and [illegible]e: Ann. méd. [illegible]ychol. 11[illegible]e 1958. 29. Reboul, E., Reboul, M. and Dorgeuille, C.: Maroc [illegible]37:784, July 1958. 30. B[illegible] Lyon méd. 200:885, Nov. 1958. 31. Lamphier, T. A.: Maryland M[illegible]7:627, Nov. 1958. 32. Leuke[illegible] Med. Klin. 53:2113, Dec. 1958.

70-95%*

of nervous, tense patients recovered or improved

For your patients, Miltown promptly checks emotional and muscular tension. Thus, you will make it easier for them to lead a normal family life and to carry on their usual work.

For you, the choice of Miltown as the tranquilizer means the comfortable assurance that it will relieve nervousness and tension without impairing your patient's mental efficiency, motor control, normal behavior or autonomic balance.

meprobamate (Wallace)

Miltown®

Supplied: 400 mg. scored tablets, 200 mg sugar-coated tablets; bottles of 50

WALLACE LABORATORIES, *New Brunswick, N. J.*

EH-8354

Continued from page 64

and Chief of Psychiatric Service at the Durham, North Carolina Veterans Hospital, has been named Professor and Chairman of the Department of Psychiatry at the University of Kentucky College of Medicine, effective this month.

Dr. Jesshill Love, Louisville, was elected President-Elect of the American Radium Society at the 41st Annual Meeting of the Society. Dr. Love has also been

Continued on page 67

CLASSIFIED ADVERTISEMENTS

WANTED—Internist. Member or board eligible to join small clinic in small Southern Virginia town. Increasing salary for two years and then partnership. Nearby teaching hospitals. New recreational facilities. Only those interested in a leisurely but stimulating group practice in small town should apply. Contact RDW, c/o SMJ.

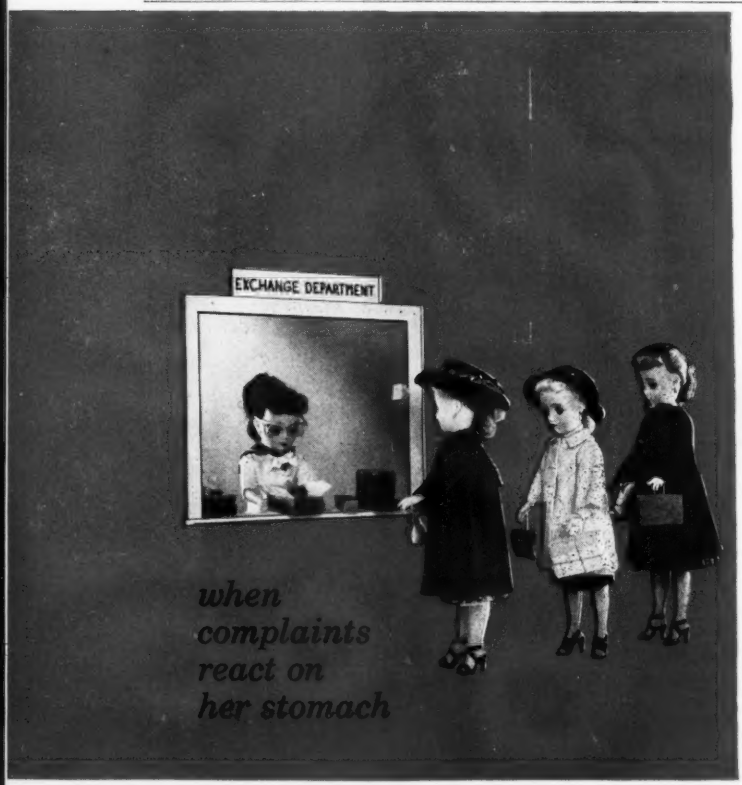
FOR RENT OR SALE—Attractive office suitable for one physician. Air-conditioned, opposite Mound Park Hospital, St. Petersburg. Telephone 52-3813 or write S. C. Swieky, 1019 - 12th Avenue, North, St. Petersburg.

WANTED—General practitioner or internist for Outpatient Department of VA Hospital, Birmingham, Alabama. New hospital, stimulating medical center atmosphere, scheduled 40-hour work week, desirable vacation and retirement benefits, good opportunity for advancement. Starting salary according to qualifications up to $11,355 per annum or $13,058 if board certified. Must be U. S. citizen. Write Director, Professional Services, VA Hospital, Birmingham, Alabama.

NEEDED IMMEDIATELY—A white physician, by a long established private sanitarium, treating nervous and mental diseases, and addiction problems. Medical man preferred. Work is with the addiction problems. Psychiatric experience preferred, not absolutely necessary. Semi-retired or retired physician not over 66 would be considered. Good salary, work not heavy. Contact BJA, c/o SMJ.

FOR SALE—Augusta, Georgia, General Practice, established 10 years; thriving industrial area, excellent hospital facilities within 1 mile; well-equipped office with complete files; reasonable rent; desirable location in medical center area; gross income over $40,000 last year; terms arranged; giving up practice to take a residency. Contact SBM, c/o SMJ.

WANTED—Radiologist, board certified or board qualified to head Radiology Service of a 479-bed GM&S hospital, located in Birmingham Medical Center and affiliated with the Medical College of Alabama. Active residency programs, desirable vacation and retirement benefits, good opportunity for advancement. Starting salary $11,355 per annum, $13,058 if board certified. Must be U. S. citizen. Write Director, Professional Services, VA Hospital, Birmingham 3, Alabama.



BUTIBEL

antispasmodic-sedat

quiets the spastic colon, through gentle dation of BUTISOL Sodium® butabarbi sodium 15 mg. and the relaxing action *natural* extract of belladonna 15 mg.

BUTIBEL TABLETS · ELIXIR · PRESTABS® BUTIBEL (Repeat Action To

McNEIL

McNEIL LABORATORIES, INC Philadelphia 32, Pa.

Continued from page 66

an active member of the Southern Medical Association since 1935.

Dr. George W. Pedigo, Jr., Louisville, has been appointed to the Board of Directors of the Kentucky Chamber of Commerce. He is the first physician ever to be so appointed. Dr. Pedigo has been recently elected President-Elect of the Jefferson County Medical Society. He is also Associate Editor of the *Journal of the Kentucky State Medical Association.*

The Annual Achievement Award of the Kentucky Academy of General Practice was presented to Dr. George S. Allen, Louisville, for his "classroom" instructions to expectant mothers.

Dr. E. C. Strode, Lexington, has been elected President of the Kentucky Chapter of the American College of Surgeons for 1959-60. He was chosen during a joint meeting with the Indiana Chapter.

Dr. Branham B. Baughman, Frankfort, has been chosen President of the Kentucky Surgical Society. He was elected at the joint meeting of the Indiana and Kentucky Chapters of the American College of Surgeons.

Dr. Daryl P. Harvey, Glasgow, has been appointed by President Dwight D. Eisenhower as a member of the President's Citizens Advisory Committee on the Fitness of American Youth. This committee, which serves in an advisory capacity to the Council on Youth Fitness, considers and evaluates "existing and prospective governmental and private measures conducive to the achievement of a happier, healthier, and more completely fit American Youth."

LOUISIANA

Dr. Jason H. Collins, New Orleans, at the annual meeting of the New Orleans Gynecological and Obstetrical Society, was installed as President. He succeeds Dr. C. Gordon Johnson. Dr. Johnson will serve as a member of the Executive Committee.

Dr. Ambrose H. Storck, New Orleans, has been re-elected Chairman of the ten state Southern Region of the American Cancer Society. He was elected at the Regional Meeting in Dallas.

Dr. Abe Mickal has been named Professor and Head of the Department of Obstetrics and Gynecology, Louisiana State University Medical School. Dr. Mickal succeeds Dr. M. L. McCall, who is to be Director of the Elizabeth Steel Magee Hospital and Chairman of the Obstetrics and Gynecology Department at the University of Pittsburgh School of Medicine.

MARYLAND

Dr. Frances B. Gordon has been elected to a three year term on the Board of Governors of the American Academy of Microbiology. Dr. Gordon, known for his studies on psittacosis, poliomyelitis, and neurotropic viruses, is head of the Division of Virology of the Naval Medical Research Institute, Bethesda.

Dr. Raymond K. Thompson, Baltimore, has re-

Continued on page 69

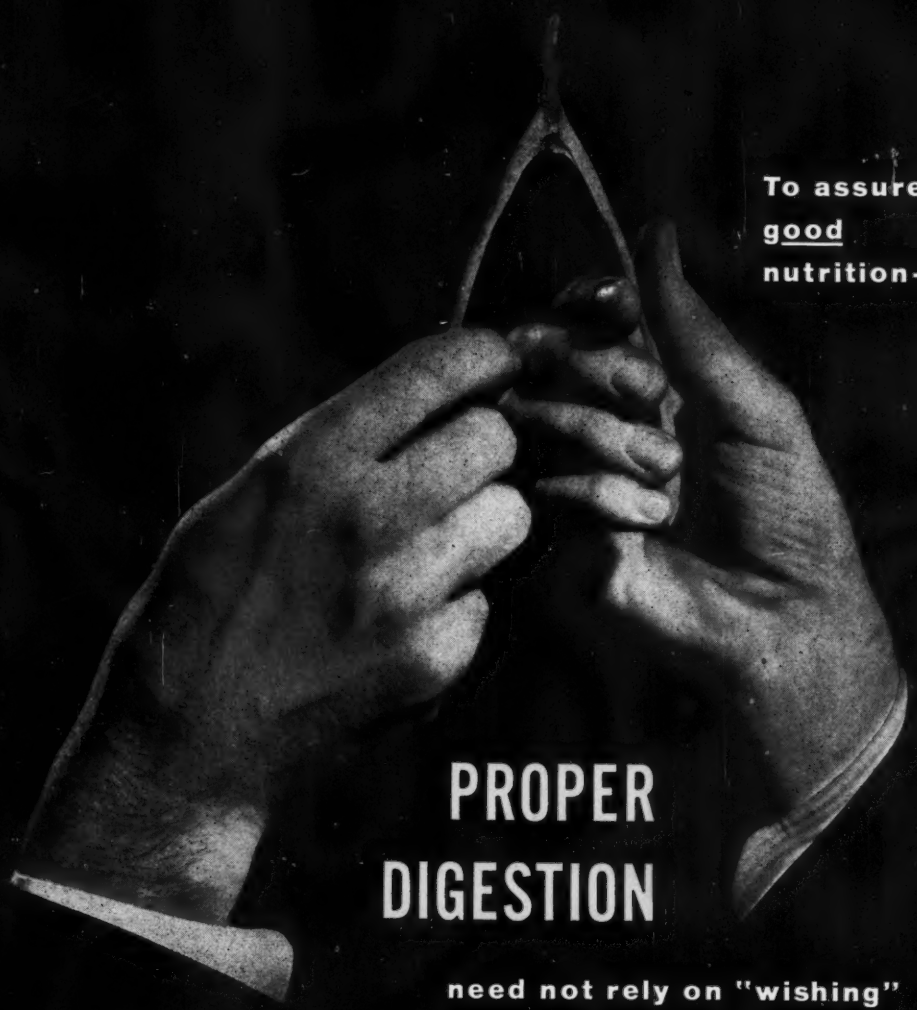
HER concepts of cleansing have changed...

Today she would prefer

TRICHOTINE®

for her most personal cleansing

THE FESLER COMPANY, INC. • 375 Fairfield Ave., Stamford, Conn.



To assure good nutrition—

PROPER DIGESTION

need not rely on "wishing"

Each double-layered Entozyme tablet contains:

Pepsin, N.F. 250 mg.
—released in the stomach from gastric-soluble outer coating of tablet.

Pancreatin, U.S.P. 300 mg.

Bile Salts 150 mg.
—released in the small intestine from enteric-coated inner core.

A. H. ROBINS CO., INC.
Richmond 20, Virginia
Ethical Pharmaceuticals of Merit since 1878

As a comprehensive supplement to deficient natural secretion of digestive enzymes, particularly in older patients, ENTOZYME effectively improves nutrition by bridging the gap between adequate ingestion and proper digestion. Among patients of all ages, it has proved helpful in chronic cholecystitis, post-cholecystectomy syndrome, subtotal gastrectomy, pancreatitis, dyspepsia, food intolerance, flatulence, nausea and chronic nutritional disturbances.

For comprehensive digestive enzyme replacement—

ENTOZYME®

Robins

Continued from page 67

turned from Ecuador, where he delivered two formal papers and conducted clinics in neurosurgery at the invitation of the Casa de Cultura Equadoriana at Quito. Dr. Thompson is Assistant Professor of Neurological Surgery at the University of Maryland School of Medicine.

MISSISSIPPI

Dr. Frank Massengill, Brookhaven, has been elected President of the Ole Miss Medical Alumni. This group meets each year during the Mississippi State Medical Association Conference. They furnish a University Medical Center headquarters for the Southern Medical Association and give a breakfast each year on Commencement morning to the graduating class of the University Medical Center.

Dr. Stanley A. Hill, Corinth, has been inaugurated as President of MSMA, and Dr. Swink Hicks, Natchez, named President-Elect. Dr. Hill is also presently serving on the Editorial Board of the Southern Medical Association.

MISSOURI

Dr. Richard A. Sutter, St. Louis, was elected President of the Central States Society of Industrial Medicine and Surgery, and Dr. William Macon, Maplewood, was elected to the Board of Governors.

Officers were elected at the annual meeting of the St. Louis Cardiac Club. They include: Dr. Christopher G. Vournas, President; Dr. Morris Alex, Vice-President; and Dr. J. A. Nuetzel, Secretary.

Ten St. Louis physicians were elected to the Board of Directors of the Institute of Medical Education and Research. Included were Drs. E. B. Williams, William Smiley, Carl J. Heifetz, Seymour Monat, Thomas E. Brittingham, William A. Tibbs, Jr., Ralph A. Kinsella, Jr., William Tomlinson, Robert E. Thomasson, and John G. Leahy.

The Washington University School of Medicine has recently announced the following promotions to Assistant Professorships: Dr. Morris Abrams, Clinical Genitourinary Surgery; Dr. Albert P. Ley, Ophthalmology; Dr. James F. Nickel, Clinical Medicine; Dr. George E. Murphy, Psychiatry; and Dr. James M. Stokes, Surgery.

Dr. Vernon E. Wilson, who is the Acting Dean of the University of Kansas School of Medicine, will become Dean of the University of Missouri School of Medicine. The announcement was made by President Elmer Ellis. Dr. Wilson's appointment is effective November 1. He succeeds Dr. Gwilyn S. Lodwick, who has been Acting Dean since March 24.

NORTH CAROLINA

Dr. Annie V. Scott, Clinical Professor of Pediatrics at the University of North Carolina School of Medicine and Pediatrician on the staff of Gravely Sanatorium in Chapel Hill, was presented by the Woman's

Continued on page 70

YOUR concepts of cleansing have changed...

Detergents are the modern, efficient way of cleansing. They provide greater surface activity and assure effective penetration.

Trichotine is the modern detergent vaginal douche. Unlike vinegar or low pH douches, Trichotine cuts through viscid leukorrheal discharge and allows complete penetration of its healing and soothing ingredients. Trichotine is bactericidal and promotes epithelization. It offers quick relief from pruritus, and its refreshing, soothing action is reassuring even to your most fastidious patients.

in vaginitis—vulvovaginitis—cervicitis—pruritus vulvae—postcoital and postmenstrual hygienic irrigation

TRICHOTINE®

write for samples and literature to **THE FESLER COMPANY, INC.** • 375 Fairfield Ave., Stamford, Conn.

Continued from page 69

Medical College of Pennsylvania with the Annual Achievement Award.

Dr. Joseph E. Markee has been appointed Assistant Dean in charge of Admissions at the Duke University Medical School. Dr. William M. Nicholson was named Assistant Dean in charge of Postgraduate Education. Dr. Markee has been Professor of Anatomy and Chairman of the Department of Anatomy, and Dr. Nicholson has been Professor of Medicine. The announcement of these appointments was made by Dean W. C. Davison.

Dr. Frank R. Lock, at the eighty-second annual session of the American Gynecological Society, was elected Treasurer of the organization. Dr. Lock is Professor and Chairman of the Department of Obstetrics and Gynecology at the Bowman Gray School of Medicine of Wake Forest College.

At the annual meeting of the American Academy of Arts and Sciences, Dr. Charles H. Burnett, Professor and Head of the Department of Medicine at the University of North Carolina School of Medicine, was elected a member of the Academy.

OKLAHOMA

Dr. Hayden H. Donahue, Oklahoma City, who is Director of Mental Health for Oklahoma and Chairman of the Oklahoma State Medical Association's Committee on Aging, has been named to serve on the National Advisory Committee for the White House Conference on Aging. He was named by Arthur S. Flemming, Secretary of Health, Education, and Welfare.

Dr. Henry H. Turner, Oklahoma City, has been installed as President of the National Society of Nuclear Medicine. The ceremonies were held at the Palmer House, Chicago, Illinois.

The Oklahoma State Radiological Society announces newly elected officers as follows: Dr. E. H. Kalmon, Oklahoma City, President; Dr. J. R. Danstrom, Oklahoma City, Vice-President; Dr. J. Murphree, Ponca City, Secretary; and Dr. V. M. Lockard, Bartlesville, Treasurer.

Dr. L. J. Spickard, Okemah, has recently been honored for his half-century of work in the medical profession by fellow physicians. Dick Graham, Executive Secretary of the Oklahoma State Medical Association, presented Dr. Spickard with a Fifty-Year Pin.

The Oklahoma Chapter of the American Psychiatric Association announces its newly elected officers as follows: Dr. George Guthrey, President; Dr. Hayden H. Donahue, President-Elect; and Dr. Jay T. Shurley, Secretary-Treasurer, all of Oklahoma City.

SOUTH CAROLINA

The Medical College of South Carolina Board of Trustees has announced three appointments and six promotions. Dr. John T. Cuttino, Charleston, will be Executive Vice-President of the Medical College; Dr. Vince Moseley, Charleston, Professor of Medicine, was appointed Associate Dean of Clinical Medicine; and Dr. Albert Cannon, Washington, D. C., was appointed

Continued on page 72

SAINT ALBANS

PSYCHIATRIC HOSPITAL

Radford, Virginia

STAFF

James P. King, M.D., Director

Daniel D. Chiles, M.D.
Clinical Director
James K. Morrow, M.D.
Clara K. Dickinson, M.D.

William D. Keck, M.D.
J. William Giesen, M.D.
Internist (Consultant)
Edward W. Gamble, III, M.D.

Clinical Psychology:
Thomas C. Camp, Ph.D.
Artie L. Sturgeon, Ph.D.

Don Phillips
Administrator

AFFILIATED CLINICS

Bluefield Mental Health Center
525 Bland St., Bluefield, W. Va.
David M. Wayne, M.D.

Beckley Mental Health Center
207½ McCreery St., Beckley, W. Va.
W. E. Wilkinson, M.D.

If they need nutritional support . . . they deserve

GEVRAL®

Vitamin-Mineral Supplement Lederle

CAPSULES—14 VITAMINS—11 MINERALS

Each capsule contains:

Vitamin A	5,000 U.S.P. Units
Vitamin D	500 U.S.P. Units
Vitamin B_{12} with AUTRINIC® Intrinsic Factor Concentrate	1/15 U.S.P. Oral Unit
Thiamine Mononitrate (B_1)	5 mg.
Riboflavin (B_2)	5 mg.
Niacinamide	15 mg
Folic Acid	1 mg.
Pyridoxine HCl (B_6)	0.5 mg.
Ca Pantothenate	5 mg.
Choline Bitartrate	50 mg.
Inositol	50 mg.
Ascorbic Acid (C)	50 mg.
Vitamin E (as tocopheryl acetates)	10 I.U.
l-Lysine Monohydrochloride	25 mg.
Rutin	25 mg.
Ferrous Fumarate	30 mg.
Iron (as Fumarate)	10 mg.
Iodine (as KI)	0.1 mg.
Calcium (as $CaHPO_4$)	157 mg.
Phosphorus (as $CaHPO_4$)	122 mg.
Boron (as $Na_2B_4O_7.10H_2O$)	0.1 mg.
Copper (as CuO)	1 mg.
Fluorine (as CaF_2)	0.1 mg.
Manganese (as MnO_2)	1 mg.
Magnesium (as MgO)	1 mg.
Potassium (as K_2SO_4)	5 mg.
Zinc (as ZnO)	0.5 mg.

LEDERLE LABORATORIES, a Division of AMERICAN CYANAMID COMPANY, Pearl River, New York

Continued from page 70

Assistant Professor of Clinical Pathology. The following faculty members were promoted to Assistant Professorships: Dr. Leon Banov, Jr., Dr. C. Capers Smith, Dr. John F. Buse, Dr. L. B. Jenkins, Dr. Eugene F. Woods, and Dr. John M. Mahaffey.

The new Charleston County Health Center will be dedicated to the county health officer, Dr. Leon Banov, Charleston. Dr. Banov has served as county health officer since 1920.

TENNESSEE

Dr. Harris L. Smith and Dr. Lorin E. Ainger, Memphis, were elected Fellows in the American Academy of Pediatrics.

Dr. Louis A. Killeffer, Harriman, was named to the State Public Health Council, and Dr. John R. Thompson, Jr., Jackson, was re-elected to the Public Health Council.

Dr. Ira M. Long, Chattanooga, has been elected President of the Chattanooga-Hamilton County Eye, Ear, Nose and Throat Society.

Newly elected officers of the Appalachian Heart Chapter include: Dr. W. A. McLeod, Johnson City, President-Elect; Dr. J. A. Knapp, Elizabethton, Vice-President; and Dr. J. B. Catron, Jr., Kingsport, Treasurer.

Dr. Samuel L. Raines, Memphis, has been re-elected Secretary-Treasurer of the American Urological Association.

Dr. B. F. Byrd, Jr., Nashville, has been elected to membership in the American Surgical Association.

Dr. Douglas H. Sprunt, Memphis, has recently been elected President of the American Association of Pathologists and Bacteriologists.

Dr. Allan Johnson, Bristol, has been elected President of the Bristol Tuberculosis Association.

Dr. Paul Morrissey, Jr., Nashville, is the newly named Chairman of the Health and Hospital Committee of the Nashville Chamber of Commerce.

Dr. Thomas F. Frist, Nashville, has been elected permanent Chairman of the Tennessee Council on Aging.

Announcement is made of three staff changes at the Medical Division of the Oak Ridge Institute of Nuclear Studies. These include the appointments of Dr. Gould A. Andrews to the post of Associate Chairman of the Division; Dr. Beecher W. Sitterson, Chief of Clinical Services; and a new addition to the staff, Dr. Ralph M. Kniseley, Pathologist. Dr. Kniseley will be Chief of Clinical Research and Training.

TEXAS

Dr. James R. Schofield has been promoted to Associate Dean of the Baylor University College of Medicine. He had previously served as Assistant Dean.

Dr. Randolph Lee Clark, Jr., Houston, has been named Chairman of the Committee on Cancer of the American College of Surgeons.

Continued on page 74

Out-Patient Clinic and Offices

HILL CREST SANITARIUM

Established in 1925

FOR NERVOUS AND MENTAL DISEASES AND ADDICTION PROBLEMS

James A. Becton, M.D. James Keen Ward, M.D.

P. O. Box 2896, Woodlawn Station, Birmingham 6, Ala. Phones WO 1-1151 and WO 1-1152

in urticaria and pruritus

VISTARIL* provides:

hydroxyzine pamoate

SPECIFIC ANTIHISTAMINIC EFFECT

in the treatment of a variety of skin disorders commonly seen in your practice.

"While some of the tranquilizers are only partially effective as far as antiallergic activities are concerned . . . [hydroxyzine] has been found, by comparison, to be the most potent thus far . . . "[2]

"The most striking results were seen in those patients with chronic urticaria of undetermined etiology."[1]

. . . reduces—erythema, excoriation, and extent of lesions.[1-4]

PSYCHOTHERAPEUTIC POTENCY

for effective relief of tension and anxiety.[1-4]

Recommended Oral Dosage: 50 mg. q.i.d. initially; increase or decrease according to individual response.

Supplied as: Vistaril Capsules—25 mg., 50 mg. and 100 mg.

Vistaril Parenteral Solution—10 cc. vials and 2 cc. Steraject® Cartridges, each cc. contains 25 mg. hydroxyzine (as the HCl).

*Trademark

More than a tranquilizer

Pfizer *Science for the world's well-being*

PFIZER LABORATORIES
Division, Chas. Pfizer & Co., Inc.
Brooklyn 6, New York

References: 1. Feinberg, A. R., et al.: J. Allergy *29*:358 (July) 1958. 2. Eisenberg, B. C.: Clin. Med. *5*:897-904 (July) 1958. 3. Robinson, H. M., Jr., et al.: J.A.M.A. *161*:604-606 (June 16) 1956. 4. Robinson, H. M., Jr., et al.: South. M. J. *50*:1282 (Oct.) 1957.

Continued from page 72

New officers of the Texas Industrial Medical Association are Dr. Max E. Johnson, San Antonio, President; Dr. Noble B. Daniel, Texarkana, President-Elect; Dr. Carl A. Nau, Galveston, First Vice-President; Dr. J. G. Burdick, Pasadena, Secretary-Treasurer; and Dr. E. E. Baden, Raymondville, new member of the Board of Directors.

The Texas Traumatic Surgical Society announces the following newly elected officers: Dr. W. D. Marrs, Port Worth, President; Dr. Edward B. Rowe, Galveston, First Vice-President; Dr. Frank H. Kidd, Dallas, Second Vice-President; and Dr. W. E. Crump, Wichita Falls, Secretary-Treasurer.

Dr. L. M. Shefts, San Antonio, has been elected President of the Texas Chapter, American College of Chest Physicians. Dr. Hiram Anderson, San Angelo, First Vice-President; Dr. Carlos J. Quintanilla, Harlingen, Second Vice-President; and Dr. John Middleton, Galveston, Secretary-Treasurer, will serve with Dr. Shefts.

The Texas Dermatological Society announces its new officers as follows: Dr. Edmund N. Walsh, Fort Worth, President; Dr. Earl Cockerell, Abilene, Vice-President; Dr. Shelton Blair, Dallas, Secretary; and Dr. William Spiller, Houston, Program Chairman.

Dr. Willard Schuessler, El Paso, has been elected President of the Texas Society of Plastic Surgeons. With him will serve Dr. John Patterson, Fort Worth, as Vice-President, and Dr. Raymond O. Brauer, Houston, Secretary.

Officers named at the Texas Neuropsychiatric Association meeting in San Antonio were Dr. Hamilton Ford, Galveston, President; Dr. Henry Gardiner, Fort Worth, Vice-President; Dr. Clarence S. Hoekstra, Dallas, President-Elect; and Dr. Ivan Bruce, Galveston, Secretary-Treasurer. Drs. Bruce Beard, Fort Worth, and Alfred H. Hill, San Antonio, were named Trustees.

VIRGINIA

The Douglas Southall Freeman award has been presented to Dr. E. Cato Drash of the University of Virginia by the Virginia Tuberculosis Association. Awards for fifty years service were presented by the Association to Drs. C. Lydon Harrell and Dr. F. R. Trigg, both of Norfolk.

Twenty-five year pins were awarded to Drs. John Wyatt Davis, Jr., and William T. Pugh at the twenty-fifth anniversary of the establishment of the Lynchburg Life Saving Crew.

Dr. W. Taliaferro Thompson, Jr., will succeed Dr. William Branch Porter as Professor and Chairman of the Department of Medicine at the Medical College of Virginia.

Dr. John R. Saunders, Richmond, has been chosen President of the District Branch Assembly of the American Psychiatric Association.

Dr. John R. Hamilton, Nassawadox, was elected to represent the Northampton County Medical Society on the Northampton-Accomack Memorial Hospital Board of Trustees.

"Brewers' yeast is an excellent source of protein of high biologic value and of the vitamins of the B complex.... When it is desired to give additional vitamins of the B complex and to add to the protein quota of the diet, this food can profitably be incorporated in other foods."*

VITA-FOOD Brewers' Yeast

an eminently valuable natural supplement — with these unique advantages:

- **Richest natural source of vitamin B complex factors plus nutritionally complete protein**
- **Optimal balance of amino acids and B complex factors**
- **Important source of minerals**

VITAMIN FOOD CO., INC. Newark 4, N. J.

*McLester, J. S., and Darby, W. J.: Nutrition and Diet in Health and Disease, ed. 6, Phila., Saunders, 1952, p. 195.

relief from all cold symptoms

Tussagesic®

decongestant, non-narcotic antitussive, analgetic, expectorant

Each timed-release tablet provides:

Triaminic®	50 mg.
(phenylpropanolamine HCl	25 mg.
pheniramine maleate	12.5 mg.
pyrilamine maleate	12.5 mg.)
Dormethan (brand of dextromethorphan HBr)	30 mg.
Terpin hydrate	180 mg.
APAP (N-acetyl-p-aminophenol)	325 mg.

Dosage: One Tussagesic tablet in the morning, mid-afternoon and evening, if needed.

Also, for patients who prefer liquid medication: TUSSAGESIC SUSPENSION.

SMITH-DORSEY • Lincoln, Nebraska
a division of The Wander Company

VESPRIN made the difference

SQUIBB TRIFLUPROMAZINE HYDROCHLORIDE

in anxiety and tension states / psychomotor agitation / phobic reactions / obsessive reactions / senile agitation / agitated depression / emotional stress associated with a wide variety of physical conditions

In the patient with anxiety and tension symptoms — Vesprin calms him down without slowing him up... and does not interfere with his working capacity. Vesprin permits tranquilization *without* oversedation, lethargy, apathy or loss of mental clarity.[4]

And Vesprin exhibits an improved therapeutic ratio — enhanced efficacy with a low incidence of side effects; no reported hypotension, extrapyramidal symptoms, blood dyscrasia or jaundice in patients treated for anxiety and tension.[1,2,3]

dosage: for "round-the-clock" control — 10 mg. to 25 mg., b.i.d.; for "once-a-day" use — 25 mg. once a day, appropriately scheduled, for therapy or prevention. **supply:** Oral Tablets, 10, 25 and 50 mg., press-coated, bottles of 50 and 500; Emulsion (Vesprin Base) — 30 cc. dropper bottles and 120 cc. bottles (10 mg./cc.). **references:** 1. Stone, H.H.: Monographs on Therapy *3*:1 (May) 1958. 2. Reeves, J.E. Postgrad. Med. *24*:687 (Dec.) 1958. 3. Burstein, F.: Clinical Research Notes *2*:3, 1959. 4. Kris, E.: Clinical Research Notes *2*:1, 1959. VESPRIN® is a Squibb Trademark

Vesprin—the tranquilizer that fills a need in every major area of medical practice

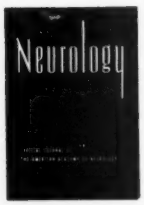
SQUIBB
Squibb Quality —
the Priceless Ingredient

QUESTION:

What have authorities reported as to the efficacy of Fiorinal in tension headache?

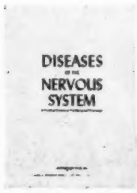
ANSWERS:

From the published reports of leading clinicians.



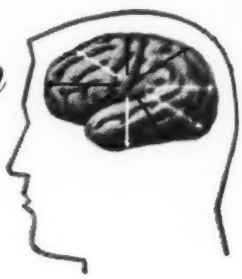
"The most effective symptomatic medication in the treatment of tension headache have been several analgesic and sedative combinations. One of the most effective is Fiorinal, which yielded relief in two out of three patients." *(Friedman, A. P., von Storch, T. J. C. and Merritt, H. H.: Neurology 4:773, Oct. 1954.)*

"In the treatment of tension headaches... [Fiorinal's non-narcotic action] offers a better opportunity for relief than some usually prescribed non-narcotic analgesics." *(Weisman, S. J.: Am. Pract. & Digest. Treat. 6:1019, July 1955.)*



"Fiorinal appears to be one of the most useful preparations to date for the relief of tension headaches. Easing of the head discomfort was accomplished by one or two tablets without any unpleasant side effects such as drowsiness or gastric upsets. In many cases Fiorinal appeared to temporarily relieve the discomfort from sinus trouble or acute respiratory infections." *(Kibbe, M. H.: Dis. Nerv. System 16:77, March 1955.)*

specific therapy for tension headache



Fiorinal®

relieves pain, muscle spasm, nervous tension

rapid action • non-narcotic • economical

FIORINAL TABLETS

Each tablet contains:
Sandoptal (Allylbarbituric acid N.F.X) 50 mg. (¾ gr.), caffeine 40 mg. (⅔ gr.), acetylsalicylic acid 200 mg. (3 gr.), acetophenetidin 130 mg. (2 gr.).

Dosage: 1 or 2 tablets every 4 hours, according to need, up to 6 per day.

SANDOZ

CO-PYRONIL™ provides quick relief that lasts and lasts

Just two or three Pulvules® Co-Pyronil daily will usually keep your hay-fever patients symptom-free and on the job all day long. Not *just* an antihistamine, Co-Pyronil is a triple combination that assures more complete relief from hay fever and other allergies.

Each Pulvule contains:

a vasoconstrictor, Clopane® Hydrochloride, to complement the action of two antihistamines by opening swollen nasal passages.

a fast-acting antihistamine, Histadyl™, to provide relief usually within fifteen to thirty minutes.

a long-acting antihistamine, Pyronil®, to maintain relief for eight to twelve hours.

Also supplied as suspension and pediatric Pulvules.

Co-Pyronil™ (pyrrobutamine compound, Lilly) Histadyl™ (thenylpyramine, Lilly)
Clopane® Hydrochloride (cyclopentamine hydrochloride, Lilly) Pyronil® (pyrrobutamine, Lilly)

ELI LILLY AND COMPANY • INDIANAPOLIS 6, INDIANA, U.S.A.

958005

"To know how to grow old is the master-work of wisdom..."

AMIEL

for your "over forty" patients prescribe

ELDEC® *KAPSEALS®*

vitamin-mineral-hormone supplement

to help fill their later years with vigor and vitality

each KAPSEAL *contains:*

vitamins	
Vitamin A	1,667 Units (0.5 mg.)
Vitamin B_1 mononitrate	0.67 mg.
Ascorbic acid	33.3 mg.
Nicotinamide	16.7 mg.
Vitamin B_2	0.67 mg.
Vitamin B_6	0.5 mg.
Vitamin B_{12} with intrinsic factor concentrate	0.033 USP Unit (oral)
Folic Acid	0.1 mg.
Choline bitartrate	6.67 mg.
Pantothenic acid (as the sodium salt)	5 mg.
minerals	
Ferrous sulfate (exsiccated)	16.7 mg.
Iodine (as potassium iodide)	0.05 mg.
Calcium carbonate	66.7 mg.
digestive enzymes	
Taka-Diastase® (Aspergillus Oryzae Enzymes)	20 mg.
Pancreatin	133.3 mg.
protein improvement factors	
l-Lysine monohydrochloride	66.7 mg.
dl-Methionine	16.7 mg.
gonadal hormones	
Methyl testosterone	1.67 mg.
Theelin	0.167 mg.

dosage: One Kapseal three times daily before meals. Female patients should follow each 21-day course with a 7-day rest interval.

packaging: ELDEC Kapseals are available in bottles of 100.

MEDICAMENTA VERA · PD & CO.

PARKE, DAVIS & COMPANY, Detroit 32, Michigan

90159